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Original Investigation

Parenchymal Pressure Inconsistency in Different Brain Areas After Kaolin Injection into the Subarachnoid Space of Neonatal Rats

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ABSTRACT

AIM: To describe the relationship between the parenchymal pressure changes and the development of hydrocephalus in kaolin-injected neonatal rats according to cerebral regions and time intervals of developing hydrocephalus.

MATERIAL and METHODS: Neonatal rats aged 2 to 3 days were examined in 5 groups as kaolin frontal "K-F", kaolin parietal "K-P", saline frontal "SF-F", saline parietal "SF-P" and control "C", based on the injected material and injection sites. All injections were performed into the cortical subarachnoid space of the right frontal and right parietal regions. The fifth group was injection free. On the 3rd, 7th, 15th, 30th and 60th days after injection, parenchymal pressures (PP) of 5-7 rats from each group were measured from different regions.

RESULTS: We compared the control group with saline-injected and kaolin-injected groups and found statistically significant parenchymal pressure differences based on regional measurements. In the kaolin groups, the mean PP values were obviously higher than the saline-injected group. Within each kaolin-injected group, the pressure values were variable and inconsistent regarding the parenchymal regions.

CONCLUSION: Hydrocephalus cannot be totally explained with existent 'bulk-flow' or 'hydrodynamic' theories. Although our experimental design was planned to develop hydrocephalus according to the bulk flow theory, our results were more compatible with the hydrodynamic theory. The present comments on the occurrence and pathogenesis of hydrocephalus are still open to debate and may require further comprehensive studies.

KEYWORDS: Cerebrospinal fluid, Hydrocephalus, Experimental, Newborn rat, Parenchymal pressure

INTRODUCTION

Hydrocephalus is the pathologic expansion of the cerebral ventricles as a disorder of cerebrospinal fluid (CSF) physiology caused by the imbalance between the production of CSF and its absorption or obstruction to bulk flow of CSF in classical comprehension (21). The other theory trying to clarify the pathogenesis of hydrocephalus is the hydrodynamic theory. According to this theory, a disorder in intracranial pulsations causes hydrocephalus. Whatever the underlying process, hydrocephalus leads to destructive consequences in various structures. Due to ventricular enlargement, a series of alterations occur within the cranial vault as structural, vascular, brain tissue, CSF and metabolic changes (2,8,15).

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Here, we discuss these theories under the light of the experiment on kaolin-induced hydrocephalic neonatal rats.

MATERIAL and METHODS

Approval for the study was granted by the Medical and Surgical Research Center of Eskisehir Osmangazi University and the Committee on Animal Experiments of the Medical Faculty of Eskisehir Osmangazi University. All experimental procedures were performed in accordance with the National Institute of Health's Principles of Laboratory Animal Care.

Animal Preparation

Sprague–Dawley neonatal rats, weighing from 6 to 7.5 g, were selected from a group of 2- to 3-days-old rats. They were divided into five groups:

Group 1: Kaolin frontal "K-F"

Group 2: Kaolin parietal "K-P"

Group 3: Saline frontal "SF-F"

Group 4: Saline parietal "SF-P"

Group 5: Control "C"

In group 1, 2, 3 and 4, the rats were secured on the table at room temperature and their scalps prepped with Betadine solution. A 26-gauge needle was inserted percutaneously under magnification, and the tip was advanced into the subarachnoid space of the right frontal region in group 1 rats, crossing the anterior edge of the fontanelle and distant from the midline. The needle tip was lodged at a 1.5-mm distance from the anterior edge of the fontanelle, and 0.03 ml of kaolin (200 mg/ml) was injected over a 5-seconds period. The needle was inserted into the subarachnoid space of the right parietal region in group 2 rats, crossing the dorsal edge of the fontanelle and distant from the midline. The needle tip was lodged at a 1.5-mm distance from the dorsal edge of the fontanelle, and 0.03 ml of kaolin (200 mg/ml) was injected over a 5-seconds period. In group 3 rats; 0.03 ml of normal saline was injected into the frontal subarachnoid space and in group 4 rats; 0.03 ml of normal saline was injected into the parietal subarachnoid space in the same fashion.

No injection was made to group 5 rats.

The kaolin in whitish color is seen easily under the dura mater. The pups were returned to their mothers after injection. For identification, numbers were marked on the backs with permanent marker. On 3rd, 7th, 15th, 30th and 60th days post injection, parenchymal pressures (PP) of 5-7 rats from each group were measured from the right frontal, left frontal, right parietal and left parietal regions. After the measurements, the animals' hearts were perfused with 10% neutral buffered formalin and they were decapitated.

Experimental Design

Anesthesia was induced by an intramuscular injection of xylazine hydrochloride (5 mg/kg) and ketamine (30 mg/kg) before parenchymal pressure measurements. Additional doses were given during the procedure as needed. Levels of $PaCO_2$, and blood pressure could not be measured in rats aged 3-15 days, because their weight and body volume were very small. In older rats, $PaCO_2$ levels and blood pressures were not measured not to contravene the standardization of the all groups. In all rats, spontaneous ventilation was maintained and rectal temperature was monitored continuously and maintained within the physiological range (37°C ± 1°C) using a heating pad (COMMAT, Turkey). The rats' heads were placed in a stabilizing apparatus and the scalp and connective tissue were excised. Heparinized (100 U/ml) saline filled catheters connected with a 3-way stopcock attached to a 23 # needle on its straight tip were used for measurement of PP from the biparietal and bifrontal areas. Parenchymal pressure measurements were monitorized and recorded via a pressure transducer as mm H_2O on a data acquisition system (Biopac MP 30, USA).

Groups and Statistical Analysis

The rats were divided into groups based on the type of injection (kaolin or saline) and the injection regions. Kaolin or saline injections were performed for all rats 2-3 days after birth. On the 3rd, 7th, 15th, 30th and 60th post injection days, 5-7 rats in each group were selected and PP measurements were performed from right frontal, left frontal, right parietal and left parietal regions. SPSS for Windows 21.0 was used in analyzing the data. The distribution of variables was checked initially by the Shapiro-Wilk test. Parametric tests were applied to data with a normal distribution. The One-way Anova Test was applied to determine the difference between independent groups. In addition, Tukey HSD Post Hoc multiple comparisons Tests were applied for checking the differences. Results were expressed as mean±std. Error and p value <0.05 was considered statistically significant. Although both right and left region pressure values were measured (Table I), we preferred to use and discuss the left frontal and left parietal region pressure values not to lead to any confusion. We thought that as all the injections were performed from the right side (right frontal and right parietal), the pressure values measured from the right might be interpreted incorrectly due to possible parenchymal lacerations.

RESULTS

Control (injection-free) group comparisons with injected groups

When the control group was compared with the SF-F group; PP measured from the left parietal region on the 7th day and from the left frontal region on the 30th day were significantly higher ($p<0.05$; respectively). When the control group was compared with the SF-P group; PP measured from the left parietal region was significantly higher on the 3rd day ($p<0.05$) (Figure 1).

When the control group was compared with the K-F group; PP measured from the left frontal region and from the left parietal region was significantly higher on the 30th day ($p<0.05$; respectively) (Figure 2). When the control group was compared with the K-P group; there was no statistically significant difference amongst PP values measured from the left parietal and left frontal regions.

The differences between days within groups according to Post Hoc Tests (Multiple Comparisons)

The differences between days in the Kaolin Frontal Group (K-F): The PP measured from the left parietal region was significantly high on the 30th day when compared with the 3rd, 7th, 15th and 60th days ($p<0.05$). There was no statistically significant difference for PP values measured from the left frontal region (Figure 3).

Table I: Parenchymal Pressure Values in Groups Regarding Post-Injection Days (mean±std. Error)

		Kaolin Frontal	Kaolin Parietal	SF Frontal	SF Parietal	Normal
3rd day	RF	2.00±0.54	9.18±4.42	2.40±0.98	1.99±0.47	0.38±0.19
	LF	1.42±0.31	2.82±0.82	1.79±0.26	1.60±0.40	0.37±0.24
	RP	1.73±0.38	7.12±4.85	2.40±0.79	1.95±0.23	0.41±0.21
	LP	1.79±0.52	6.97±4.56	3.26±0.68	4.16±0.93	0.54±0.26
7th day	RF	2.43±0.74	2.52±0.91	2.94±1.46	0.96±0.34	0.38±0.19
	LF	2.26±0.73	2.12±0.28	1.50±0.44	0.72±0.35	0.37±0.24
	RP	2.65±0.71	8.60±2.49	6.55±2.22	3.79±1.92	0.41±0.21
	LP	2.67±0.78	10.73±3.19	6.10±2.71	3.28±1.50	0.54±0.26
15th day	RF	1.24±0.66	16.75±6.04	0.41±0.41	0.92±0.40	0.38±0.19
	LF	2.32±1.69	7.90±4.38	1.61±0.71	0.85±0.62	0.37±0.24
	RP	1.44±0.44	10.78±3.98	2.58±1.18	5.95±4.59	0.41±0.21
	LP	3.19±1.91	7.38±3.24	2.12±0.94	1.78±0.71	0.54±0.26
30th day	RF	3.10±0.50 y	28.08±7.33 x	0.75±0.42	1.44±0.53	0.38±0.19
	LF	3.58±0.31	17±51±9.48	2.33±0.50	1.29±0.43	0.37±0.24
	RP	4.56±1.34	11.00±6.50	4.51±2.91	2.97±2.32	0.41±0.21
	LP	10.80±3.13	12.18±6.51	1.97±0.55	1.73±0.55	0.54±0.26
60th day	RF	0.50±0.21	25.96±9.87 x	0.76±0.29	1.17±0.36	0.38±0.19
	LF	0.92±0.49	15.77±5.68	2.02±0.43	1.10±0.50	0.37±0.24
	RP	1.52±0.43	15.94±3.26 x	2.03±0.32	1.17±0.47	0.41±0.21
	LP	1.55±0.43	7.47±2.59	1.82±0.93	1.21±0.52	0.54±0.26

(RF: Right Frontal, LF: Left Frontal, RP: Right Parietal, LP: Left Parietal)

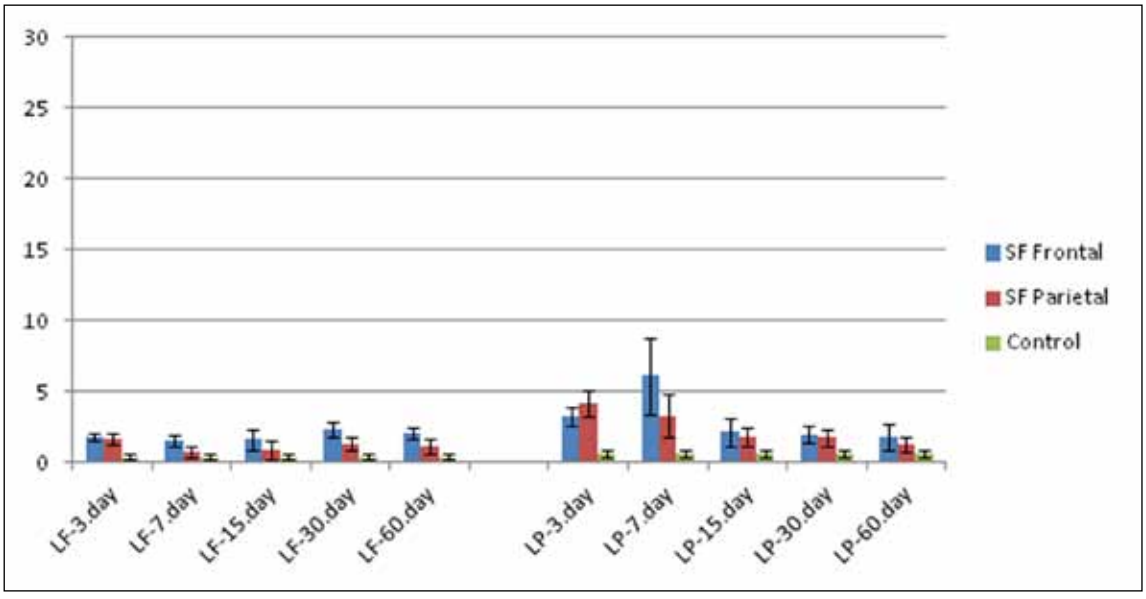

Figure 1: Parenchymal pressure comparisons of SF groups with control groups.

The differences between days in Kaolin Parietal (K-P), SF-Frontal (SF-F) and SF-Parietal (SF-P) Groups: There were no statistically significant differences for PP values between days in the K-P, SF-F and SF-P groups.

Pressure differences between regions regarding post injection days

There were no statistically significant differences between all regions on the 3rd, 7th, 15th and 30th days among all groups. Although the pressure values began to decrease especially after the 30th post-injection day among the Kaolin groups, the left frontal pressure was significantly higher in the K-P group when compared with the K-F and SF-P groups ($p<0.05$) (Figure 4).

DISCUSSION

The present study intends to describe the relationship between the development of hydrocephalus and the parenchymal pressure changes regarding the cerebral regions in neonatal rats.

On the 3rd, 7th, 15th, 30th and 60th post-injection days, the parenchymal pressures of 5-7 rats were measured from each group from the right frontal, left frontal, right parietal and left parietal regions. Although, both right and left region pressure values were measured, we preferred to evaluate and discuss the left frontal and left parietal region pressure values not to lead to any confusion because all the injections were performed from the right side (right frontal and right parietal) and the pressure values measured from the right could be interpreted incorrectly due to probable cortical lacerations. In our study, we preferred to use neonatal rats for inducing hydrocephalus

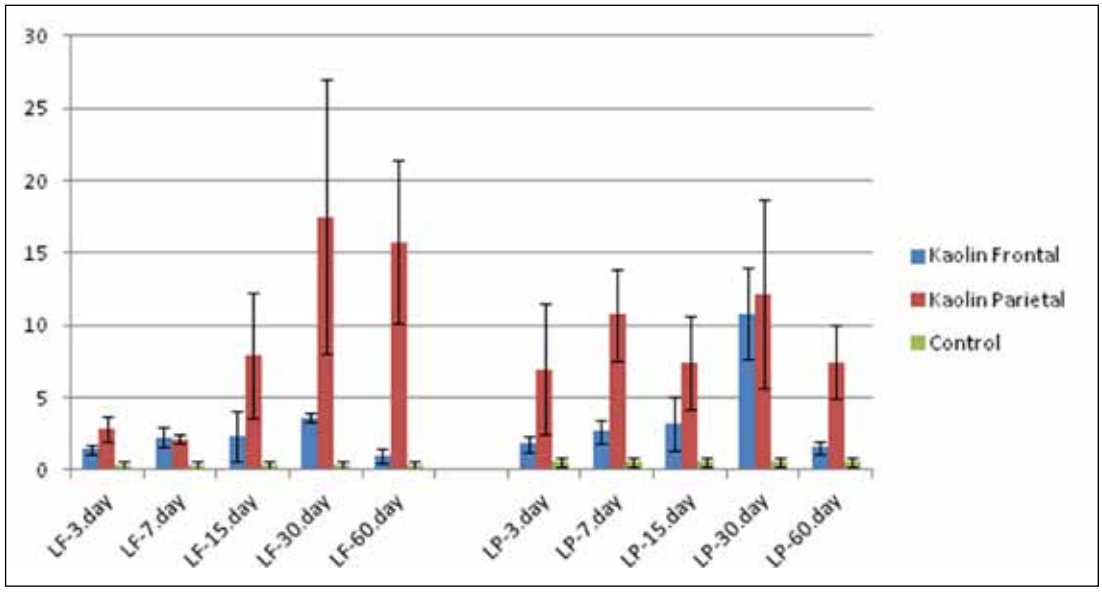

Figure 2: Parenchymal pressure comparisons of Kaolin groups with control groups.

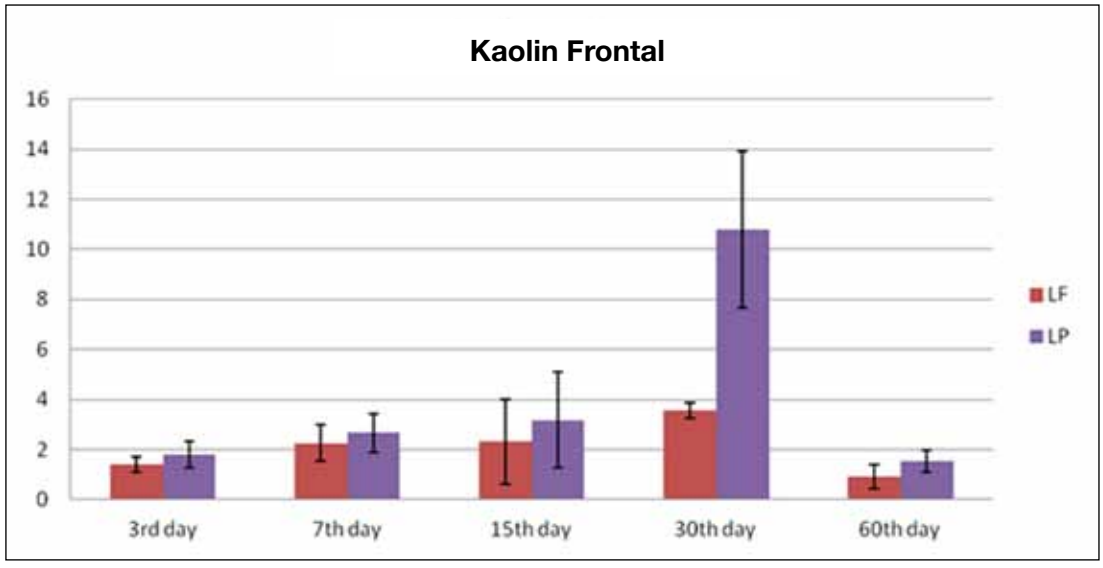

Figure 3: The parenchymal pressure measured from left parietal region was significantly higher on the 30th day when compared with 3rd, 7th, 15th and 60th days ($p<0.05$). (**LF:** Left frontal, **LP:** Left parietal).

because their brains are in the process of growth and thus are more susceptible to induced structural changes. Compared to the adult brain, young brains are believed to have greater plasticity.

The craniums of neonatal rats at 2 to 3 days of age have open sutures and fontanelles, and their scalps are transparent (6). We could thus check the localization of the tip of the needle easily. In addition, we chose to use kaolin injection into cortical subarachnoid space to develop communicating hydrocephalus. Previously described hydrocephalus models include kaolin injection into the basal cistern, and into the ventricle and cisterna magna (6,9,13,18,22). Ventricular and cisterna magna injections develop non-communicating hydrocephalus. In clinical terms, communicating hydrocephalus is the most widely seen type and the underlying mechanism is still controversial. Although basal cistern injection causes communicating hydrocephalus, it is not so easy to perform and needs experience not to harm the brainstem and surrounding neural structures or vasculature. For basal cistern injection, the time to gain sufficient qualification may be questionable and besides this technique is not applicable for neonatal rats. In our rats, kaolin-reactive fibrosis at the convexity produced arachnoid adhesions on the cortical surface and resulted in a realistic progressive hydrocephalus. Developing hydrocephalus was confirmed with both postmortem brain sections and clinical findings of the animals, i.e. increasing

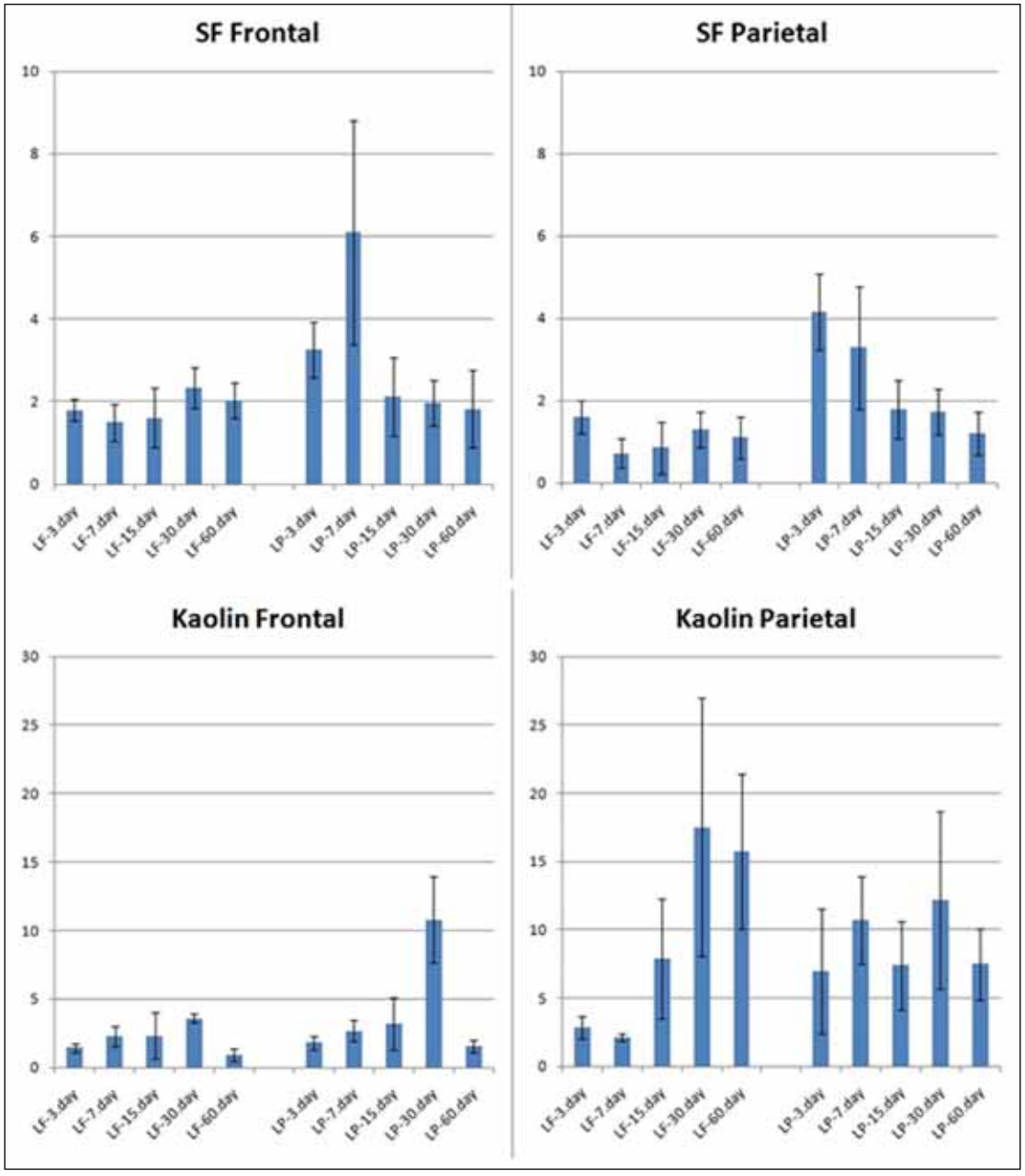

Figure 4: Parenchymal pressure changes within groups between days in the measured regions.

head size, diminished activity, patency and tenseness of the fontanelle. After decapitation of the rats, brain sections were examined on coronal plane sections.

In our study, we focused on regional brain parenchymal pressure changes. To our knowledge, this is the only experimental study on regional parenchymal pressure changes in cortical subarachnoid kaolin-induced communicating hydrocephalus on neonatal rats. We compared control groups with SF-injected and Kaolin-injected groups. When SF groups (SF-Frontal and SF-parietal) were compared with control group; the pressure values measured from the parietal regions were higher in the first few days (3rd and 7th) of injection and subsequently decreased to normal values in the following days. However, in frontal region measurements, significantly increased pressure levels were detected on the 30th day. This inconsistency in the SF groups may be attributed to high standard deviation values. When the Kaolin-Frontal group was compared with the control group; the only statistically significant high pressure levels were measured the from left frontal and left parietal regions on the 30th day. However, there was no statistically significant difference between these measurements from the left parietal and left frontal regions. In the Kaolin-Parietal group, although the left frontal and left parietal pressure values showed distinct variations in every group, there were no statistically significant differences when compared with the control group, probably due to high standard deviation levels. Although 150 rats were decapitated, the limited rat quantity in the groups might be the reason for these high standard deviation levels. This problem may be solved in future studies by increasing the number of rats in each group.

The pressures began to decrease after the 30th day in every region in all Kaolin groups. However, in the SF-injected groups, the pressure alterations were not compatible with this finding. Although we made this comment according to mean±std error values, we observed that the pressures continued to increase in particular rats in the Kaolin groups. This observation can be explained by impaired cerebral autoregulation secondary to persistent high intracranial pressure and shifting the compensatory phase to the decompensatory phase (1,3,5,14). The damaged Windkessel phenomenon that provides and maintains constant blood flow to arterioles and capillaries during diastole under normal conditions may be attributed to this unwilling process (3,5). And in further stages, ventriculomegaly persists with high intracranial pressure. However, if the Windkessel phenomenon is able to recover (in brains with favorable compliance capacity), ventriculomegaly may not accompany the high pressure values and may proceed to normal pressure hydrocephalus (14).

None of the SF injected rats developed hydrocephalus by the time. Brain sections from the 3rd and the 7th day of kaolin-injected rats showed no hydrocephalus either. After the 15th day, only 1 of 14 rats showed suspicious ventricular enlargement. On the 30th day, almost all of the rats showed hydrocephalus in kaolin groups. These results are very similar to our department's previous studies (6,7). On the other hand, these findings are not similar to the results of Li et al. (18). Li et al. also applied the same cortical subarachnoid kaolin injection, but the rats did not develop hydrocephalus for 3 to 4 months (18). This major difference between these experiments might be attributed to Cosan et al.'s model that was not applied in adult but neonatal rats.

Whatever the underlying pathogenesis, both communicating and non-communicating hydrocephalus are characterized by pathological dilation of ventricles, leading to parenchymal damage especially in periventricular white matter in the earliest stage (10,17). There are two theories to enlighten the pathogenesis of hydrocephalus. The oldest and widely accepted one is the bulk-flow theory. The newest one, questioning the bulk-flow theory, is the hydrodynamic theory. Bulk-flow of CSF is very important for its circulation within the ventricles and cisterns but arterial pulsation is necessarily needed to mobilize the CSF. The CSF bulk flow theory explains hydrocephalus as an imbalance between the pathways of CSF formation and absorption. An obstruction to the CSF outflow outside the ventricular system causes communicating hydrocephalus (i.e. obstruction due to kaolin injection at the pacchionian granulations) (11,12,19,21,23). Although the bulk-flow theory easily defines hydrocephalus, there are some squares that need to be filled in the clinical hydrocephalus puzzle. Many authors have considered this issue and made valuable observations and interpretations regarding the hydrodynamic theory (11,12). Greitz demonstrated that the major absorption site of the CSF is the capillaries of the central nervous system, contrary to popular belief (12).

Although our study design seems to be based on the bulk-flow theory to explain the pathogenesis of communicating hydrocephalus, our results stand closer to the hydrodynamic theory. The regional parenchymal pressure differences we have detected in Kaolin-injected rats can be explained by the hydrodynamic theory. In the experimental kaolin-induced hydrocephalus model, Penn et al. measured high ventricular, subarachnoid and parenchymal pressures without any regional differences (20). We measured parenchymal pressures from different regions of the brain and detected different pressure values within the same rats at the same time. In our opinion, this could be explained, according to the hydrodynamic theory, by the existence of varying amounts and denseness of cerebral vasculature in the frontal and parietal regions. Cavaglia et al. demonstrated that the vascular density of rat brain is higher in the parietal region when compared with the frontal region in their study of quantitative analysis of vascular density (4). As the vascular network is denser in the parietal than the frontal region (4) and as the arterial pulsatility reflection to the arterioles and the capillary circulation is the principle underlying cause of the communicating hydrocephalus hypothesis of Egnor et al. (11), our results might be in concordance with this theory (11,16).

The limitations of our study are;

1. Due to the paucity of the rats in groups, statistical analyses revealed high standard deviation values. Because of this reason, although the comparisons were marked in some group, they were not statistically significant.

2. We did not measure pressure from the subarachnoid space

and ventricles because of extremely narrow structures of neonatal rats. In a study of Penn et al., they measured pressures from intraventricular, subarachnoid space and brain parenchyma in their kaolin-induced hydrocephalus experiment in adult dogs. They found no pressure gradients between these areas either during the acute phase or in the long term (20).

3. We only focused on parenchymal pressure differences. We did not perform light microscopy examination and ventricular size index calculation, because in our previous experiments we have shown the aforementioned subjects clearly (6,7).

CONCLUSION

The hydrodynamic perspective on the mechanism indicates that the vascular and parenchymal pressure alterations may be the real cause of the progression in hydrocephalus. Tissue compliance variations will possibly be attributed to this theory. The present comments on the occurrence and pathogenesis of hydrocephalus are still open to debate and may require further comprehensive studies. The pressure inconsistency in different parenchymal regions in our study may need further explications in the light of hydrodynamic or/and bulk flow viewpoint.

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