Original Article

The Third Ventricle in Kaolin-induced Hydrocephalus in Juvenile Rats

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Abstract

Background: The enlargement of the third ventricle in hydrocephalus has mechanical effects on the structures that form its boundaries such as thalamus and hypothalamus. This may explain some of the symptoms associated with hydrocephalus. While the lateral ventricles had been widely investigated in hydrocephalus, studies of the third ventricle are sparse. The present study set out to investigate the ependymal lining and the direction of enlargement of the third ventricle in hydrocephalus. **Materials and Methods:** Three-week old rats were divided into 6 groups (A-F) of five each. Groups A-C were experimental and sacrificed after 1, 4, and 8 weeks of induction, respectively, while groups D-F served as age-matched controls. Hydrocephalus was induced by intracisternal injection of 0.04 ml of 200 mg/ml kaolin suspension. Rats were sacrificed by cervical dislocation and approximately 1 mm thick coronal brain slices were obtained at optic chiasma level. Slices were fixed in 10% formal saline, processed and stained with hematoxylin and eosin. **Results:** Compared with corresponding control rats, the lateral ventricle width was significantly increased in 1 and 8 weeks postinduction experimental rats ($P = 0.005$ and 0.012 respectively), while supero-inferior distance of the experimental third ventricle was significantly lower at 1-week postinduction ($P < 0.001$), and increased at 8-week postinduction ($P = 0.025$). However, differences in the inter-thalamic distance at 1- and 8-week were not statistically significant ($P = 0.14$ and 0.224, respectively). Ependymal detachment was patchy and generalized at 1 and 4 weeks, respectively. Thinned and detached ependymal lining were noted 8-week postinduction. **Conclusion:** Kaolin-induced hydrocephalus caused early ependymal detachment in the third ventricle of rats, while ependymal thinning and villi sparing was a feature of chronicity. The third ventricle enlarges in the supero-inferior direction, this might explain some symptoms associated with hydrocephalus.

Key words: Cilia, ependymal lining, hydrocephalus, lateral ventricle, third ventricle

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Introduction

The flow of the cerebrospinal fluid (CSF) from the lateral ventricles through the third ventricle to the fourth ventricle is propelled by the ciliated ependymal layer that lines the surface of the ventricles. The ependymal lining of the ventricle is also essential for the restriction of the CSF within the ventricular system.[1] Anomalies of the ependymal lining of the ventricles will result in a distortion of the dynamics of CSF flow. Such anomaly is a frequent cause of hydrocephalus.[2] Triventricular hydrocephalus is related to the lack of ependymal flow following distorted ependymal cilia.[3]

Triventricular hydrocephalus is demonstrated as the dilation of the lateral ventricles and the third ventricle,[4] revealing the involvement of the third ventricle in the morphological derangements associated with hydrocephalus. The third ventricle is a diencephalic midline structure with its anterior wall formed by the lamina terminalis, its floor formed by the hypothalamus while the thalami formed its lateral walls.[5] The roof is formed by the fornix overlaid by vascular structures.[6,7] Atresia of the third ventricle cavity is very rare.[8] Dilated third ventricle has been reported in cases of congenital hydrocephalus.[5] Hypothalamic-pituitary gland dysfunction is associated with the lesions of the anterior and inferior boundaries of the third ventricle. Chronic hydrocephalus and increased intracranial pressure can result in anatomical changes in the floor of the third ventricle.[9] Ventral distention of the floor of the third ventricle is associated with obstructive hydrocephalus. This is

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a reflection of the pressure gradient between the third ventricle and basal cisterns.[10] Striking dilation of the lateral, third, and fourth ventricles was reported in α-adducin–null mice study[11] reinforcing the assertion that third ventricular dilation and distortion occur alongside the severally reported dilation of the lateral ventricle in hydrocephalus. The third ventriculostomy is very helpful in the management of obstructive hydrocephalus.[4] Though endoscopic ventriculostomy is a simple procedure that is very efficient in the management of hydrocephalus, a distortion of the anatomy of the floor of the third ventricle might portend grave danger for the procedure.[9] Some communicating hydrocephalus has been found to involve the enlargement of the third ventricle, and there is the possibility of employing the third ventriculostomy in their management. The floor of the third ventricle contains little or no neuronal cells.[12] The thinned wall of the third ventricle has, however, been suspected to contain neuronal cells that could explain some consequences of endoscopic ventriculostomy. This is in addition to suspected injury to the hypothalamic-pituitary structures which are part of the inferior boundary of the third ventricle.[13] In the adult, pathology of structures around the third ventricle has resulted in cognitive changes.[14,15] They participate in the normal neurodevelopmental process and are responsible for cognitive skills, attention, verbal performance, and visuospatial functions[16,17] In trisomy 21, the width of the third ventricle predicts the extent of impairment of the above stated functions,[15] and can serve as a reliable cognitive prognostic tool.[18] An association has been established between the diameter of the third ventricle obtained by transcranial ultrasonography and neuropsychological disability in multiple sclerosis.[18]

Despite the involvement of the third ventricle in the pathology in hydrocephalus, it is the distortions of the lateral ventricle anatomy in experimental hydrocephalus that have enjoyed intense research interest and reportage, while the description of the morphological distortion of the third ventricle and that of its choroid plexus (CP) and ependymal lining have not been extensively reported. The critical roles of structures such as thalamus that form the lateral wall of the third ventricle is a justification for the assessment of the third ventricle in the acute and chronic states of kaolin-induced hydrocephalus in juvenile rats in the present study.

Materials and Methods

Animals and groupings

Healthy juvenile rats, aged 3 weeks were weaned and used for the study following ethical approval obtained from the University of Ibadan Animal Care and Use Research Ethics Committee. The rats were divided into six groups as follows:

- Group A: Were induced at 3 weeks and sacrificed 1-week postinduction
- Group B: Were induced at 3 weeks and sacrificed 4 weeks postinduction
- Group C: Were induced at 3 weeks and sacrificed 8 weeks postinduction
- Group D: Were control rats for experimental group A sacrificed at the age of 4 weeks
- Group E: Were control rats for experimental group B sacrificed at the age of 7 weeks
- Group F: Were control rats for experimental group C sacrificed at the age of 11 weeks.

The rats were kept in plastic cages in a well-aerated animal holding of the Department of Anatomy and Cell Biology, Obafemi Awolowo University, Ile-Ife, Nigeria. The light and dark cycles were natural and beddings were changed frequently. Water and rat chow were provided *ad libitum*.

Induction, sacrifice and tissue harvesting

Acid washed Kaolin powder, obtained from Hopkins and Williams, England, was dissolved in normal saline to make a suspension of 200 mg/ml. The rats were anesthetized intramuscularly with ketamine in the dose of 90 mg/kg body weight and diazepam at 12.5 mg/kg body weight. A total of 0.04 ml of the kaolin suspension was injected percutaneously through the cisterna magnum with a 25G needle mounted on insulin syringe. The induced rats were closely monitored. Moistened rat chows were provided in the first 24 h postinduction. Subsequently, normal rat chow and water were made available.

The rats were sacrificed by cervical dislocation at the end of the stated weeks. The rats were perfused through the hearts (cardiac perfused) with 10% formal saline and then decapitated. The brain was carefully harvested and sectioned coronally at the level of the optic chiasma. Coronal brain slices of approximately 1 mm thick were obtained and further immersion fixed in 10% formal saline and then processed for light microscopy.

Paraffin sections of 5 μm thick were obtained using Leica RM 2125 microtome (Leica microsystem, Germany) and stained with hematoxylin and eosin stain. Photomicrographs were taken with Leica DM 750 microscope interfaced with Leica ICC50 digital camera. Dimensions of the lateral ventricle were measured at the level of the *Cornus ammonis* 1 of the hippocampus. The length of the third ventricle was measured from its roof where the CP hangs to its floor in the midline. The width of the third ventricle (inter-thalamic distance) was measured as the distance between the 2 thalamic bulges at their summits. All measurements were taken with the use of Leica application suite software.

Measurements were presented as means and standard error of the mean. Statistical difference was determined with Student's *t*-test. Photomicrographs were presented in low and high magnifications.

Results

A total of 30 healthy juvenile rats, aged 3 weeks were weaned and used for the study. The rats were divided into six groups of five each, as described under methods.

General observation

The lethargic effect of anesthesia lasted for about 24 h after induction. The rats had reduced motor activity and feeding was reduced during this period. Feeding and motor activities improved after 24 h in the control rats. Experimental rats, however, remained lethargic and feeding only improved gradually toward the end of the 1st week of induction.

Enlargement in the third and lateral ventricles

Table I shows the dimensions of the lateral and third ventricles at 1 and 8 weeks. There was a significant increase in the width of lateral ventricle at the end of 1st and 8th weeks after induction in experimental rats compared to the controls. The third ventricle, however, revealed a significant reduction in the distance from roof to floor (length) in the experimental rats compared with the controls at the end of 1st postinduction week, while a significant increase in the length of the third ventricle was noted in the experimental rats at 8 weeks postinduction. In both groups, the difference in the inter-thalamic distance was not statistically significant.

Choroid plexus and ependymal layer

Photomicrographs of the third ventricles at 1, 4, and 8 weeks are presented in Figures 1-3. Florid and normal CP was noted in the experimental and control rats at 1-week postinduction [Figure 1]. The lining of the third ventricle revealed a single layer of ependymal cells with demonstrable villi. A focal pseudostratification of ependymal cells was noted in the experimental rats. Other regions of the ependymal layer showed multiple layering and disorganization of the ependymal cells [Figure 1].

Photomicrographs of the third ventricles 4 weeks after induction are shown in Figure 2. The CP appeared florid and the ependymal lining revealed a single layer of cell in the villi in the control rats. Though the CP remained florid in the experimental rats, there was, however, detachment of the ependymal layer from the surrounding thalamic structure with demonstrable interependymal space with regions of double ependymal layer.

Photomicrographs of the third ventricles 8 weeks after induction are shown in Figure 3. In 8 weeks after induction group, the CP was florid in the control and experimental rats. In addition, the ependymal layer was well laid out with villi in the control group while the experimental group revealed a thinned out ependymal layer with the focal presence of villi.

Discussion

While the rats in the control and experimental groups were lethargic for about 24 h postanesthesia injection, only the hydrocephalic rats remained lethargic beyond this period suggesting that the post 24-h lethargy was likely to be the effect of the kaolin-induced hydrocephalus as against that of the anesthesia. Ventricular enlargement might take some time to develop in a kaolin-induced hydrocephalus in the rat model, motor defects appeared to have commenced early, whether or not this was as a result of pressure build in the ventricle prior to obvious ventricular enlargement or a consequence of an outright degenerating effect on neuronal morphology or function in such early stage will be a worthwhile venture for further investigation. Such early manifestations of lethargy have been reported in a human model of hydrocephalus.[19,20]

The CP is the apparatus for the production of CSF. This is achieved specifically by the epithelium of the CP, which is a component of the blood-CSF-brain barrier.[21] The present study showed a uniformly florid CP in the controls and rats with kaolin-induced hydrocephalus across the different age groups, indicating the absence of anatomical

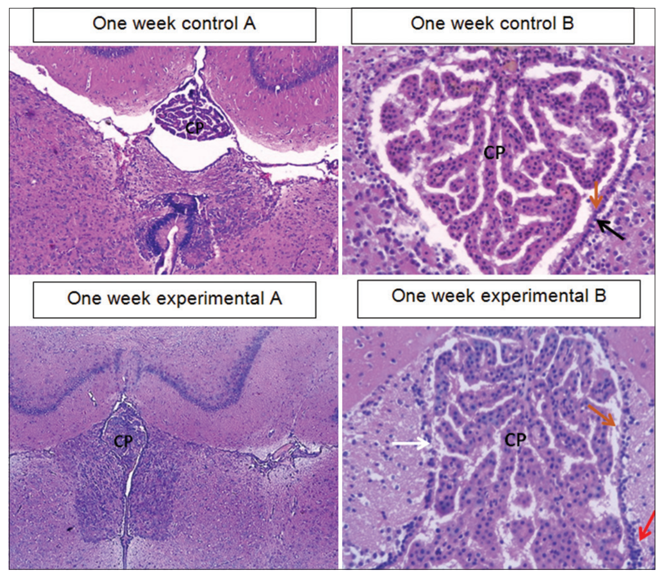

Figure 1: Photomicrographs of the third ventricles of control (C) and experimental (E) rats at 1-week, showing the choroid plexus, ependymal layer discontinuity (white arrow), region of pseudostratification of ependymal cells (red arrow), normal ependymal layer (black arrow) and villi (Brown arrow). Stain H and E; A: ×100; B: ×400.

Table I: Dimensions of the lateral and third ventricles at 1 and 8 weeks

Duration	Groups of rats	Mean (SEM)		
		Lateral ventricle width in mm	Third ventricle length in mm	Inter-thalamic distance in mm
1 week	Control (*n*=5)	0.103 (0.016)	0.749 (0.024)	0.353 (0.047)
	Experimental (*n*=5)	0.204 (0.021)*	0.396 (0.028)*	0.256 (0.036)
8 weeks	Control (*n*=5)	0.146 (0.008)	0.500 (0.010)	0.344 (0.019)
	Experimental (*n*=5)	0.255 (0.033)*	0.681 (0.065)*	0.437 (0.068)

*Statistically significant at $P<0.05$. SEM: Standard error of mean

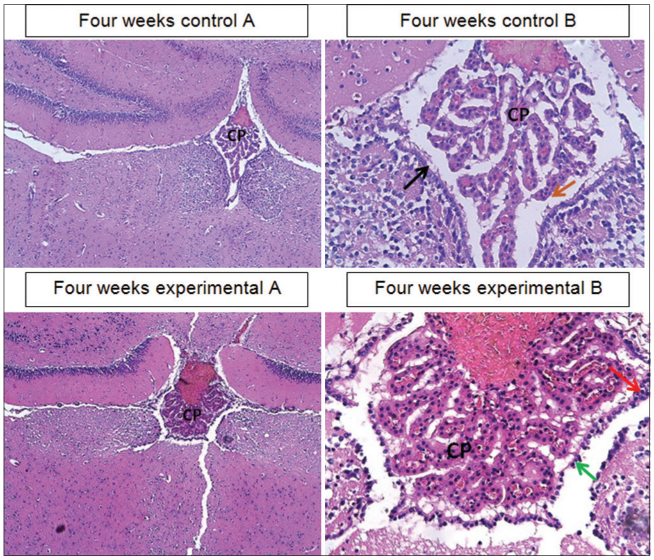

Figure 2: Photomicrographs of the third ventricles of control (C) and experimental (E) rats at 4 weeks, showing choroid plexus, normal ependymal layer (black arrow), detached ependymal layer (green arrow), region of pseudo-stratification of ependymal cells (red arrow) and Villi (brown arrow). Stain H and E; A: ×100; B: ×400.

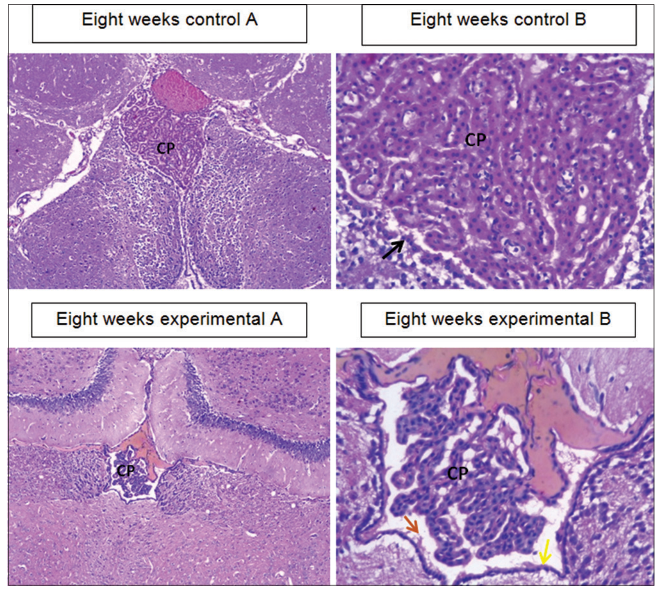

Figure 3: Photomicrographs of the third ventricles of control (C) and experimental (E) rats at 8 weeks, showing choroid plexus, normal ependymal layer (black arrow), thinned ependymal layer (yellow arrow) and normal villi (brown arrow). Stain H and E; A: ×100; B: ×400.

changes of the third ventricle CP within the 1st 8 weeks of kaolin-induced hydrocephalus in the rat model. The implication of this finding is that the altered production of the CSF in kaolin-induced hydrocephalus was not likely to be secondary to the morphological anomaly of the CP. However, a structural anomaly of the CP secondary to aging had been reported.[22] While absorption of the CSF by the arachnoid villi is significantly impaired in the chronic phase of canine model of hydrocephalus[23] the preservation of the third ventricle CP even after 8 weeks of hydrocephalus in the present study pointed to a possible structural explanation for the increasing build of CSF pressure in hydrocephalus.

While the control rats demonstrated an intact ependymal lining across the 3 age groups, the anomaly of the ventricular lining was noted in all the experimental groups. Several discontinuations of ependymal lining of the third ventricle was were demonstrated as early as the 1st week after kaolin injection. Though controversy may exist as to whether ependymal denudation was an effect or cause of different models of hydrocephalus, the findings of the present study showed that early anomaly of the ependymal lining in the third ventricle was a feature of kaolin-induced hydrocephalus. Aside from the focal discontinuity of the ependymal lining, a pseudostratification of the ependymal cells was also noted in the third ventricle of the rats 1-week after kaolin injection. This represented the early features of ependymal pathology. Similar pseudostratification of the ependymal layer was noted in the spinal cord of humans with congenital hydrocephalus.[24] Such ependymal rosette is a feature of ependymoma.[25] 4 weeks after kaolin injection ependymal lining of the third ventricle detached from the underlying thalamic and hypothalamic tissue. The detachment of the ventricular lining presented two distinct layers of ependymal cells with a demonstrable intra-ependymal space. While the inner layer of ependymal cells appears complete and intact, the outer layer appears incomplete and patchy with the floor of the third ventricle devoid of any ependymal lining. Such detachment would expose the underlying tissues to the CSF, which might be toxic to the cellular composition of the regions. The exposure of the floor of the third ventricle makes the hypothalamus and infundibulum more likely to be thus exposed. Eight weeks after kaolin injection, the ependymal lining of the third ventricle appeared thinned out with patchy detachment from the underlying thalamic tissue. Denudation of the lateral ventricle ependymal layer had been associated with the loss of germinal ependymal zone, abnormal neuronal migration as well as the disorganization of the subventricular zone.[26] Therefore, the detachment and thinning of the ependymal layer in the third ventricle might result in similar anomalies, leading to the cellular disorganization of the thalamus and hypothalamus, a reduced capacity to regenerate and a distortion of the thalamic and hypothalamic neuronal migration. A detachment of the ependymal layer had been associated with the abnormalities of adhesion molecules.[27]

Whether this will be true of the ependymal of the third ventricle will be a worthy of future research focus. The range of anomalies associated with the ependymal lining of the third ventricle may result from the exposure of the underlying thalamic and hypothalamic tissue to the CSF resulting in cellular injury to the region as previously reported in the lateral ventricle of the hydrocephalic rats.[28,29] Anomalies of the ependymal lining and its cilia have been reported in several studies of hydrocephalus.[30-32] Most of these reports have been with respect to the lateral ventricle. The persistence of the villi despite morphological changes in the ependymal lining in the present study showed that the villi-deforming effect of hydrocephalus was not present in all the parts of the ventricular system. Sloughing of the ependymal lining had been attributed to the build-up pressure within the ventricular system.[30] The findings in the present study, therefore, showed that the increased ventricular pressure in kaolin-induced hydrocephalus was not evenly distributed. Such differential response of the various parts of the ventricular system had been noted in the aqueduct of a mice model of congenital hydrocephalus.[33] Since the structure of villi of the ependymal lining is the same across the different ventricles, the possible difference in the ventricular pressure in the third ventricle was the probable mechanism underlying the persistence of villi, while sloughing of the villi had been reported in several studies on the lateral ventricles of rats with hydrocephalus.

While the differences between the inter-thalamic distances of the third ventricle in the control and experimental rats were not significant, a significant reduction in the distance between the roof and the floor of the third ventricle (length) in the experimental rats was noted 1-week after kaolin injection. A significant increase in the length of the third ventricle was noted in the experimental rats 8 weeks after kaolin injection. This revealed that the distension of the third ventricle appears to be in the supero-inferior direction as against lateral direction. A lateral distension might have resulted in the disruption of the cellular composition of the thalamus, which forms the lateral walls of the third ventricle thereby causing a distortion of several somatosensory impulse-related functions. However, the distension of the third ventricle as shown in the directions of the roof and floor of the third ventricle might explain the sustained lethargy noted in the present study. This is because a distension of the floor of the third ventricle will likely affect the hypothalamus which is known to affect consciousness in addition to other vital functions. Anomaly of the pituitary functions in hydrocephalus and the subsequent reversal after surgical intervention[34] gave credence to the suspicion that distention of the third ventricle might result in the disruption of the functions of structures on the floor of the ventricle, further pointing to a supero-inferior distension of the third ventricle.

Kaolin-induced hydrocephalus is an obstructive model of the anomalies that result in ventriculomegaly due to increased ventricular pressure. The present study revealed denudation and detachment of the ependymal lining of the third ventricle leading to the exposure of the underlying structures such as the thalamus and hypothalamus to CSF causing possible cellular disruption and toxicity. The injury to the ependymal lining of the third ventricle got worse as the duration of the hydrocephalus increases possibly due to the mechanical effect of the ventriculomegaly of the third ventricle. However, the villi of the ependymal lining appeared to be preserved 8 weeks after kaolin injection. In addition, the present study showed that the distension of the third ventricle was in the supero-inferior direction thereby leading to the vulnerability of structures that were related to the floor and roof of the ventricle. This might be a pointer to the possible anatomical explanation of the various symptoms associated with hydrocephalus.

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Conflicts of interest

There are no conflicts of interest.

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