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Mathernal diabetes chenges aqueduct of sylyius volume in newborn rats

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Abstract

Maternal diabetes is associated with an increased risk of several complications in the offspring. In present study, we examined the effects of maternal diabetes on the volume of aqueduct of Sylvius (A canal in the midbrain connecting the third and fourth ventricles) in newborn Wistar rats. At 7th day of pregnancy hyperglycemia was induced by a single injection (i.p.) of streptozotocin (55 mg kg^{-1}). Control animals were given an equal volume of citrate buffer. After parturition 1 pup were randomly selected from each litter, their brain dissected, fixed in 10% formalin, sectioned in 7 ìm thicknesses and stained by H.E. By applying stereological techniques and systematic random sampling scheme the volume of the brain aqueduct of Sylvius were estimated. In comparison with controls, statistical analysis showed significant increases ($p<0.05$) in the volume of the brain aqueduct of Sylvius. In conclusion it seems that, maternal diabetes effect on blood brain barrier permeability in newborn rats that could cause large amount of CSF generation. These effects could lead to brain disorders such as hydrocephalus.

Key words: Aqueduct of Sylvius, maternal diabetes, CSF

Introduction

Offspring of mothers with diabetes mellitus remain at risk for fetal hyperinsulinemia, consequent increase fetal adiposity and often excess fetal size (macrosomia) which increases the likelihood birth trauma and operative delivery. In addition, many studies indicate that maternal metabolic abnormalities seen in gestational and preexisting diabetes have long term consequences on weight and pancreatic function and neurologic development of the offspring(1).Extensive experimental and clinical evidence indicates that metabolic disturbances in the mother contribute to virtual all the adverse effects of DM on the offspring(2).In addition to a number of developmental abnormality in structure and function of CNS, It has been reported that diabetes increase normal pressure hydrocephalus(3).Hydrocephalus is caused by excessive retention or production of cerebrospinal fluid (CSF) which is produced by the choroidal epithelial cells of the choroid plexus(4).

Mathernal diabetes is associated with an increased risk of several complications in the offspring, such as growth disturbances and congenital malformations (5). Diabetes Mellitus is a chronic progressive disease that often results in vascular complications, including the development of microangiopathy, which is characterized by basement membrane thickening (6) cytoskeleton rearrangement and increased paracellular leakage (7). Extensive research has been conducted on endothelial cell dysfunction in a number of tissues, including kidney, peripheral nerve, retina, heart and skeletal muscle (8). Also, diabetes increases blood brain barrier permeability (9) and is a risk factor for normal pressure hydrocephalus. Normal pressure hydrocephalus occurs when the volume of CSF increases, but it is pressure remains normal or just slightly elevated (10). Hydrocephalus is a net accumulation of CSF. Hydrocephalus results from an alteration of a normal physiological process and has multiple causes.

With the rare exception of CSF overproduction from a choroids plexus papilloma, all types of hydrocephalus are either communicating or non-communicating (11). In non-communicating hydrocephalus, impairment of CSF flow is within the ventricular system whereas in communicating hydrocephalus, the impairment is distal to the ventricles, mostly in the subarachnoid space (12). Non-communicating hydrocephalus results from lesions such as aqueductal occlusion, obstruction of the outlets of the fourth ventricles, tumors adjacent to the ventricular wall, hemorrhage and infection within the ventricular system (11). Most of infant from diabetic mother suffer from hydrocephaly and problems related to that. This study investigated the effects of maternal diabetes on the volume of aqueduct of Sylvius in newborn**.**

Material and method

All chemical used in this study were purchased from Sigma (UK)**.**

Experimental design

Wistar rats were used for this study. The study was approved by the committee of our institute. Young adult female rats (approximately 250 gr) were maintained at 22c with 12-h periods of light and darkness. They were mated with normal males and the morning of appearance of vaginal plug was considered day 0 of gestation. At 7 days of gestation (dg),diabetes was induced by a single injection(i.p.) of streptozotocin (55mg/kg)dissolved in sterile phosphate buffered salin (13). Control group received only buffer. Then animals were housed under standard condition and received food and water. Induction of diabetes was confirmed by blood glucose level (glycemia > 400). After birth one pups of each mother were selected for stereological analysis of C.P.

Blood assays

Blood samples were collected from mothers after delivery of the pups and the levels of glucose, uric

acid , urea, Ca and P by autoanalyser were measured.

Sampling

Under the pentobarbital anesthesia the newborn brain was rapidly removed and fixed in 10% paraformaldehyde. For histological evaluation samples were placed in same fixative overnight and were embedded in paraffin. Serial cross –sections were cut and stained with hematoxylin and eosin. The volume of aqueduct of Sylvius were measured with Cavalieri method (14). All experiments were performed a minimum of two times.

Statistical analysis

Student's t test was used for comparison when only two groups were analyzed. Statistical significance was chosen as $p<0.05$. All results are reported as Mean ± SEM.

Results

Blood chemistry

Diabetes were assessed in this study by monitoring the blood glucose levels in both PBS and STZ injected rats (Table 1).There was a significant increase ($p<0.001$) in blood glucose levels from (100±5 mg/dL) in control to (470±18 mg/ml) in diabetic rats. In addition there was a meaningful increase ($p<0.05$) between cholesterol, urea, uric acid, [P] and [Ca] levels of diabetic mothers plasma and control mothers.

Ca	P	Cholestrol	Triglycerides	Urea	Uric asid	Cratinin	Glucose	
8/2±0/1	5/45± 0/4	47/13±2/7	119/8±22	18±1/6	1/91±0/1	0/46±0/03	100± 5	contol
8/95±0/25*	7/53±0/5*	87/38±7/6*	216/9±49	28±2*	5/48±0/7*	0/53±0/06	470±18*	diabetic

Table.1: Concentrations of different metabolites in normal and diabetic rat serum

values are means ± SEM, n=6.
$p<0.05$ indicates significant difference from control determined by Student's t test

Volume of aqueduct of Sylvius

There was a signeficent decrease ($p<0.01$) in the aqueduct of Sylvius volume from newborn of diabetic mothers in comparison to the control ones. This increase was (0.614±0.99) mm^3 in control to (1.0415±0.2) mm^3 in newborn from diabetic mothers.

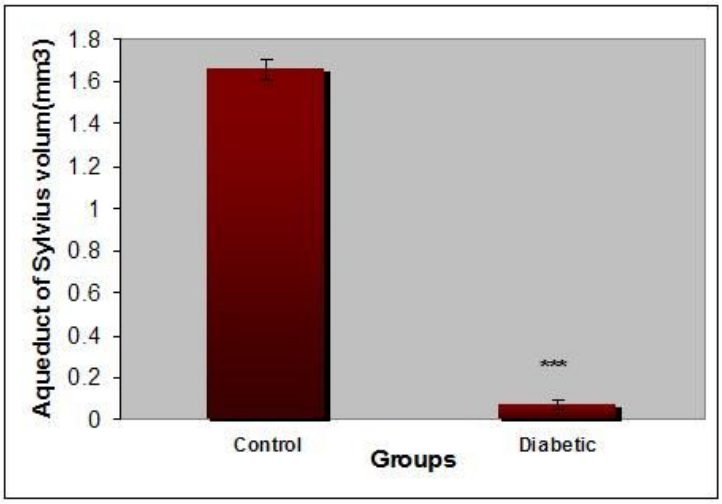

FIG.1. Comparing aqueduct of Sylvius volume in the neonates from diabetic and control rats.

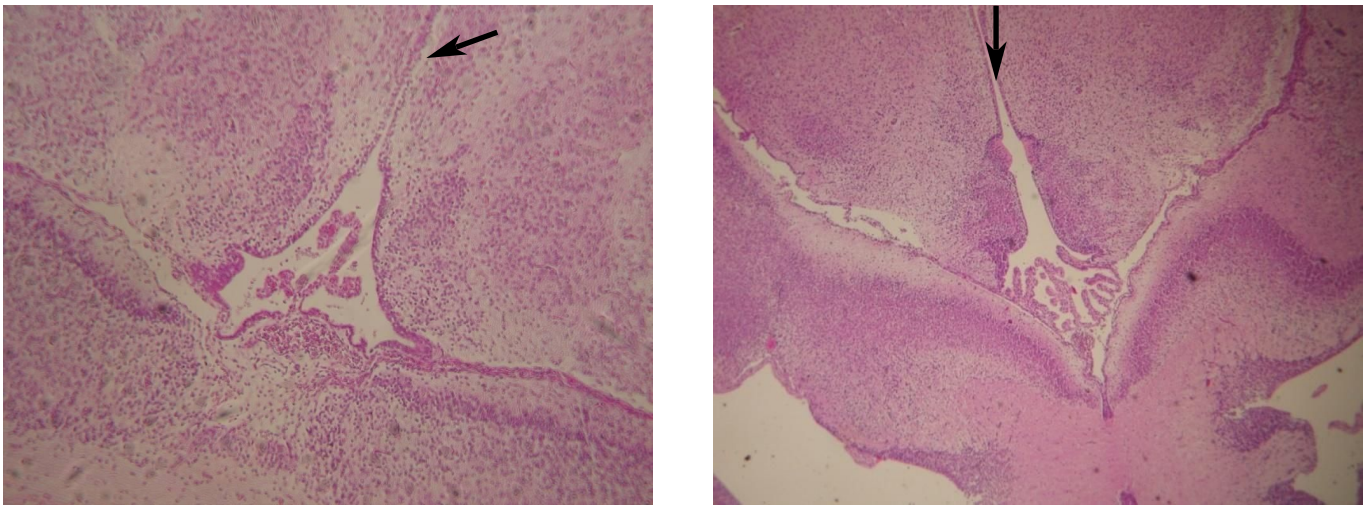

FIG.2. Cross section of aqueduct of Sylvius in neonate rat (X200). Spikes show the aqueduct of Sylvius.
Left : neonate from diabetic mother - Right: neonate from control mother

Discussion

Data indicate that there is a significant change in the blood glucose in different groups. In newborn from diabetic mothers, there was a significant decrease ($p<0.01$) in the aqueduct of Sylvius volume in comparison to the control ones (Fig. 1). In microscopyic slid, remarkably clear that the aqueduct of Sylvius was closure (Fig. 2).

The present study was high risk for hydrocephaly in newborns from diabetic mothers. Earlier studies have suggested that increased glucose lead to malformation. In addition, oxidative stress disturbances in the polyol pathway and prostaglandin metabolism have been proposed to induce diabetic abnormally (15).

It has been suggested that enhanced activity of PKC may be a common feature of all diabetic complications (16). In other site, it seems likely that if the drainage systems at the base of the brain are inadequate by design or become obstructed from aging or injury, which it could eventually lead to hydrodynamic failure and chronic NPH (10). In this type of hydrocephalus, the brain would fill from the bottom up. The structure that would fill first would be the subarachnoid spaces and basal cisterns. The location and size of the cisterns and subarachnoid space gives them a greater capacity to absorb excess CSF (17). After the cisterns become overfilled, the ventricles start to fill up. When they become overfilled they begin to stretch eventually they become enlarged (18).

Many reports have dealt with the probable functions of the SCO-RF complex (11). One of the working hypotheses relates the SCO to the circulation of CSF. During the fetal life, the material secreted by the SCO into the ventricular CSF prevents the closure of the Sylvain aqueduct, thus allowing the CSF to circulate freely between the third and fourth ventricle. A maldevelopment of the SCO might lead to the aqueductal stenosis and a congenital hydrocephalus. Hyperglycemia alters physiological condition to pathological. We are still in the process of understanding the pathophysiological mechanisms underlying hydrocephalus in infants from diabetic mothers.

In total, it is concluded that maternal diabetes effect on blood brain barrier permeability in newborn rats that could cause large amount of CSF generation. These effects could lead to brain disorders such as hydrocephalus or hyperglycemia, stenosed sylvain aqueduct.

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