CLINICAL AND PATHOMORPHOLOGICAL DATA ON HYDROCEPHALUS CAUSED BY PRENATAL INFECTION BY THE LYMPHOCYTIC CHORIOMENINGITIS VIRUS


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The first case of probable prenatal infection caused by the lymphocytic choriomeningitis virus was described by Komrower, et al. in 1955 [1]. The mother became ill 12 days before delivery and the infant on the 7th day of life. The infant died 5 days later with symptoms of meningitis and subarachnoidal hemorrhaging, which the authors believed was possibly due to cisternal puncture. The mother's diagnosis of lymphocytic choriomeningitis was made serologically and the child diagnosis was confirmed by isolation of the virus.

Ackermann, et al. [2] and M. M. Sheynbergas, et al. [3] in 1974 independently reported of cases of serologically confirmed prenatal infection caused by lymphocytic choriomeningitis virus that induced the development of hydrocephalus. These authors described a total of 16 cases of congenital hydrocephalus, one case of infantile cerebral paralysis, isolated right-sided blepharoptosis and abortion associated with prenatal infection caused by the lymphocytic choriomeningitis virus. The majority of these children had foci of chorioretinal degeneration [2-6].

In addition to clinical and immunological data, this work cites the first results of a pathomorphological study on two cases of congenital hydrocephalus due to infection caused by

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**Numbers in margin indicate pagination in original foreign text.
the lymphocytic choriomeningitis virus.

Patient Yu. Ya. was born on October 22, 1974 of healthy young parents as the first pregnancy. At the 4th month of pregnancy, the mother had a flu-like illness with high temperature and strong headache for a week. During labor, fetal hydrocephalus was established and ventricular puncture was performed to facilitate delivery. About 1100 ml of transparent fluid was released. The newborn weighed 4100 g and the head circumference was 42 cm. The infant was discharged from the maternity hospital on the 7th day.

Hydrocephalus subsequently progressed continually. The circumference of the head at age 1 month equalled 47.5 cm, at 4 months 64 cm and at 14 months 68.5 cm. A symptom of "setting sun", divergent squint and significant psychomotor lagging were noted at age 5 months. The infant still reacted to sounds, smiled in response to speech and freely moved its limbs. Fatness was normal. Symptoms of cerebral insufficiency, however, developed further: muscle hypertension of the limbs and tetraparesis.

Study of the eyes revealed myopia: the right eye was 3 diopters and the left eye 6 diopters. The pattern of the optic fundus: papillae of the visual nerves of pale gray color with distinct boundaries. The arteries and veins of the retina were of medium diameter and untwisted. In the central part of the retina of both eyes there was one distinctly blackened large (2½ diameters of the visual nerve papilla) chorioretinal white foci with slight quantity of pigment on its edges. Vessels were not determined in these foci.
A craniogram showed that the bones of the cranium were flat, thin and difficult to distinguish; the basal fossae were smooth.

The child was sent at age 6 months to a group for invalid children.

The serological data showed: Wasserman reactions and bonding of the complement with toxoplasma antigen were negative. The child's serum was studied three times for the presence of immunofluorescent antibodies for the lymphocytic choriomeningitis virus [7]: at age 3 days, 8 months and 15 months the titers equalled respectively 1:256, 1:256 and 1:512. These antibodies in a 1:32 titer were also found in the postmortem study of the liquor. Within 3 days after delivery the mother's titer of immunofluorescent antibodies for the lymphocytic choriomeningitis virus was 1:4, and repeated studies at 5 and 8 months after delivery did not reveal more antibodies. High antibody titers in the child indicate prenatal infection caused by lymphocytic choriomeningitis virus while the low antibody titer in the mother indicates that she had an infection caused by this virus no less than 5 months ago [4]. We can assume that lymphocytic choriomeningitis in the mother occurred in the form of severe flu-like illness in the 4th month of pregnancy.

The child died at age 15 months from decompensated hydrocephalus and pneumonia.

Autopsy showed that the large cerebral hemispheres had the appearance of thin-walled sack with very dilated lateral and III ventricles which contained about 3 l of transparent liquor. Under the ependyma of the lateral ventricles foci
were found of slightly pronounced hemosiderosis. The aqueduct of Sylvius was closed. The soft cerebral membrane commissures also were present in the area of apertures of Lushki and Mazhandi.

Histological study of the soft cerebral membranes noted single lymphoid cells. In the large cerebral hemispheres there was edema of the endothelium of the small blood vessels, in places proliferation of the endothelial cells and plasmorrhagia in the mass of the walls. The vascular lumen was constricted in places. Perivascular edema was severe. In places there were deposits of brown pigment with single lymphoid cells on the circumference, indicating the presence of lymphocellular capillaritis. There were more pronounced lymphocellular infiltrates in the zone of the aqueduct of Sylvius. Neuronal nuclei were clear with signs of central chromatolysis. In the area of the bottom of the IV ventricle there was lysis of individual neurons and their groups. Nerve fiber cytoplasm was loose with signs of hyperchromicity. Ependymal cells were partially desquamated. In the vascular plexus, in the intervascular spaces there was infiltration by single lymphocytes and their groups. Damage to their endothelium was noted and the lumen was filled with erythrocytic-leukocytic thromboses.

Patient M was born on September 19, 1974. The mother was 42-years-old, the father 29. The daughter was the second pregnancy, and the first child had been born healthy. During pregnancy the mother did not have any illness accompanied by high temperature. Labor began on time and the infant was born by Caesarian section due to oblique position. The newborn weighed 3700 g, was 53 cm long and the circumference of the head was 40 cm. The infant was discharged from the maternity hospital on the 11th day with circumference of the head
enlarged by 1.5 cm, tremor of the hands and elevated leg muscle tone. She entered the hospital at age 1 month 11 days. Symptom of "setting sun" and tetraparesis were noted. The head circumference was 47 cm (at 2 months 50.5 cm). X-ray of the cranium did not reveal additional shadows, the relief of the cranial vault was smooth and the base was depressed.

Ophthalmoscopic data showed: disks of the visual nerves were yellow-gray with boundaries slightly shaded from the medial side. The arteries and veins of the retina did not show peculiarities. In the central part and on the periphery of the retina there were white chorioretinal foci pigmented on the edges with distinct boundaries of slightly varying size.

Within 10 days after admission, the condition of the child deteriorated. Purulent otoantritis was found. Hemolytic plasmocoagulating staphylococcus resistant to the antibiotics used was found in the pus from the ear.

The liquor obtained twice during the second month of life was transparent, the Pandi reaction was ++, ++++, protein 46 and 66 mg per 100 ml, sugar 28 and 31 mg%, chlorides 827 and 640 mg%, cells both times were 10/3 (in normal limits). In the fourth month of life, however, the liquor changed severely. It became slightly turbid, the protein content increased to 1840 mg per 100 ml, the number of cells to 2080/3 and 75 - 95% of these cells were lymphocytes. During life bacteria were not removed from the liquor, and hemolytic staphylococcus was sifted out only from the liquor taken during autopsy.

The Wasserman reactions and bonding of complement with toxoplasma antigen were negative.
The child was first studied for immunofluorescent antibodies for the lymphocytic choriomeningitis virus at age 8 days, then twice more, at age 2 months and 3 months; the titers respectively equalled 1:256, 1:256 and 1:1024. The liquor was studied during the four months of the child's life six times and once postmortem. The titers fluctuated between 1:256 and 1:512. Immunofluorescent antibodies in the mother's serum were studied once within 8 days after delivery and the titer was 1:32.

Antrotomy was performed on the child on March 26, 1975 and pus was found in both antriums. The child died on April 1 at age 4½ months. A week before death the child's head began to diminish and retraction of the fontanels and seams was noted.

Autopsy, in addition to cranial deformation noted adhesion of the solid cerebral membrane with periosteum of the vault bones. Under the adhesions were residues of substantia medullaris 0.5 - 1.0 cm thick. The lateral and III cerebral ventricles were dilated the maximum, essentially comprising one cavity filled with yellowish-whitish fluid with gray flakes floating in it. Some of the fibrinous clusters adhered to the inner surface of the ventricles. The aqueduct of Sylvius was impassable because of adhesions. The cerebellum and the IV cerebral ventricle did not have visible changes.

Histological study of the soft cerebral membranes noted infiltration of them by lymphoid cells, in places with admixture of single cells and those arranged in groups of the plasma series, mainly mature plasmocytes. In the tissue of the large cerebral hemispheres there was a dominance of the proliferative component. The endothelial cells of the blood
vessels proliferate, in the mass of the walls there was plasmorrhagia, as a result of which the vascular walls look thickened while the lumen looks constricted. These symptoms were more pronounced in the submeningeal regions of the cerebral hemispheres where the small cerebral vessels often were completely obliterated. The glial component of the cerebral tissue was in a state of proliferation. Numerous diffusely arranged infiltrates from the lymphoid cells were observed, in places with admixture of plasmocytes.

The cytoplasm of the pyramid cells was very granular, in places it was foamy with symptoms of cellular lysis. The architectonics of the cerebral tissue was disrupted. Study of the cerebral tissue in the area of constriction of the aqueduct of Sylvius noted especially pronounced proliferation of glial cells. The ependymal cells of the ventricles proliferate, in places the ependyma was completely disappeared. In the vascular plexus there was abundant infiltration by mononuclears, which was especially pronounced perivascularly where signs of sclerosing were also revealed.

V. R. Purin and T. P. Zhukova [8] considered that among congenital forms of hydrocephalus of infectious origin only those forms of hydrocephalus which were due to syphilis, toxoplasmosis or cytomegalia could occupy an independent place. Studies of Ackermann, et al, [2] and M. M. Sheynbergas, et al. [3-5] demonstrated that the infection caused by the lymphocytic choriomeningitis virus has to be added to this list.

The course of illness in the two cases we have described was severe. The main reason for decompensation and relatively rapid unfavorable development of the disease was blockage of the liquor passages. In the same way as in the majority of
other cases of prenatal infection caused by the lymphocytic choriomeningitis virus, foci of chorioretinal degeneration were also revealed in the patients described.

An immunological feature in the first case (patient Yu.) was the relatively longer persistence of immunofluorescent antibodies in high titer before the onset of the fatal outcome at age 15 months. In other examined children with prenatal lymphocytic choriomeningitis, these antibodies were also highly active for a longer time than in postnatal lymphocytic choriomeningitis, however their titer dropped severely by the end of the first year of life [4].

Patient M had another immunological feature: the titers of immunofluorescent antibodies for the lymphocytic choriomeningitis virus in the liquor were as high as in the serum. In all other children, as well as in all studied cases of postnatal infection caused by the lymphocytic choriomeningitis virus, the titers in the liquor were significantly (4 - 64 times) lower than in the serum. High titers in the liquor apparently indicate that the immunofluorescent antibodies of this child were not only passed through the hematoencephalic barrier, but were also actively formed in the central nervous system.

Morphological changes deserve especial attention because they have been described for the first time in children who died from hydrocephalus whose etiological relationship to the lymphocytic choriomeningitis virus had been precisely established. There is a published description of several cases of postnatal lymphocytic choriomeningitis that ended fatally [9]. Primary symptoms in these cases were inflammation of the soft cerebral membrane, vascular plexus and ependyma.
accompanied by lymphocytic infiltration [10]. We found similar changes in the cases we have described. Features of tissue reaction at the same time were revealed in each of them. Patient Yu. had a dominance of the alternative element of the pathology with damage to the vascular walls, ependymal cells for a great extent, as well as neurocytic clasmatoysis all the way to karyolysis. The lymphocellular reaction in this case was moderate and there were a lot of segmentonuclear leukocytes among the lymphoid cells. The alternative component of damage in patient M was less pronounced. In addition to lymphocytes there were many macrophages among the cellular elements, as well as plasma cells and the reaction of glial elements was active. Activity of local production of antibodies expressed as exceptionally high titers of the immunofluorescent antibodies for the virus of lymphocytic choriomeningitis in the liquor apparently corresponded to this morphological substrate.

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