BRAIN TUMORS OF THE CHOROID PLEXUS INDUCED BY AVIAN MYELOBLASTOSIS VIRUS

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In the last 30-35 years much progress has been made in the development of methods of obtaining tumors of the brain and its accessory organs (meninges, vessels, choroid plexuses, ependyma). It has been shown that tumors of the CNS can be obtained by grafting fragments of it [4], by the use of chemically pure carcinogens [6-8] or radioactive isotopes [5], and by inoculation of certain viruses into the brain. Most experimental studies have involved the use of Rous sarcoma virus [1, 11, 15], murine polyoma virus [13], various adenoviruses [2, 3], bovine papilloma virus [10], etc. However, none of the above-mentioned viruses has been inoculated. Of the whole range of these viruses only simian virus 40 (SV-40) gave rise to pathological changes in this organ.

The aim of this investigation was to induce tumors of the choroid plexus of the brain with avian myeloblastosis virus (AMV), which until recently has been regarded as a purely leukemogenic factor.

EXPERIMENTAL METHOD

The virus used was a commercial preparation of AMV, strain BAJ-A, produced by the Institute of Poliomyelitis and Virus Encephalitis, Academy of Medical Sciences of the USSR. The titer of the virus after preliminary intravenous passage through highly susceptible chicks was required to be 10^9-10^{12} PFU/ml. Experiments were carried out on chicks highly susceptible to AMF (White Leghorn, Enney cross) and noninbred chicks aged 1 and 2 days. After mild stunning of the chicks with ether they were inoculated with 0.01-0.02 ml of material from a tuberculin

TABLE 1. Tumor-like Diseases and Tomurs of the Choroid Plaxuses and Other Brain Tumors Induced in Chicks by AMV

Experimental conditions	Number of chicks	Material inoculated	Dose, ml	Mode of injection	Choroid epithelioma of choriod plexuses			Diseases of meninges (meningiomas)	Other CNS tumors	Tumor-like hyperplastic processes
					initial stage	fully developed stage	atypical stage			
Experiment										
Enney cross	33	AMV	0,01—0,02	Intracerebral	2	2	2	40	—	—
noninbred	75	AMV	0,01	»	5	4	7	42		2
Total . .	108	—	—	—	7	6	9	82	—	2
Control										
Enney cross (7 days)	3	AMV	0,01	Intracerebral	—	—	—	—	—	—
Enney cross	11	AMV	0,1	Intravenous	1	1	1	—	—	2
white Leghorn	3	AMV	0,1	Intravenous	—	—	—	—	—	—
noninbred	7	AMV	0,1		—	—	—	—	2*	1
Enney cross	4	RSV	0,01	Intracerebral	—	—	—	—	3**	
noninbred	6	Healthy chick serum	0,01		—	—	—	—	—	—
Total . . .	34	—	—	—	1	1	1	—	5	3
Grand total . . .	142	—	—	—	8	7	10	82	5	5

Legend. RSV) Rous sarcoma virus; *) undifferentiated CNS tumors; **) Rous sarcomas.

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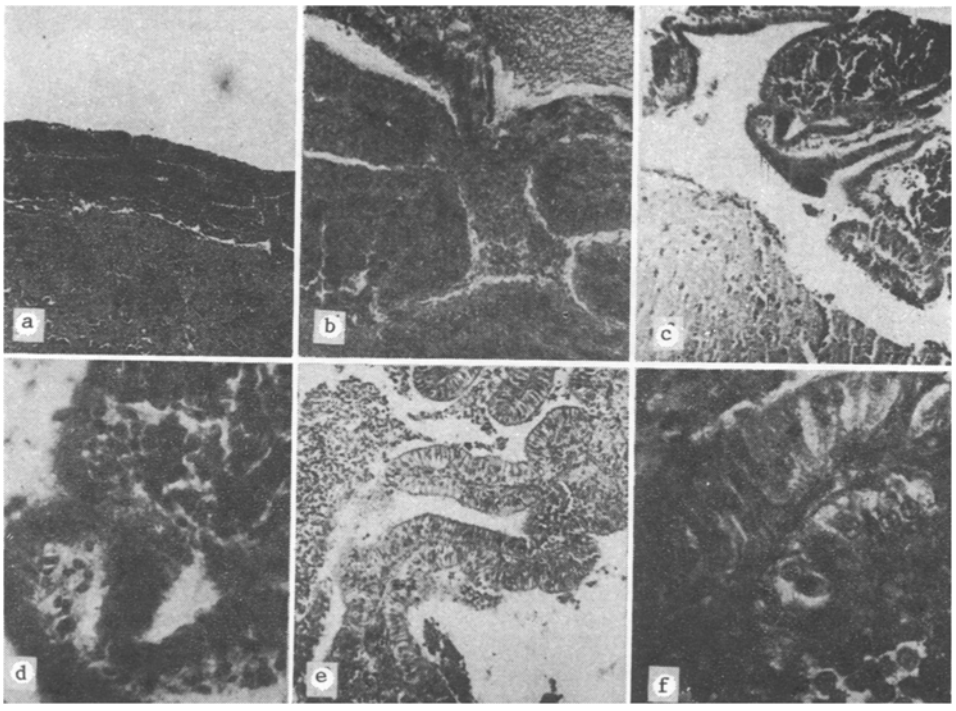

Fig. 1. First and second stages of development of tumors of the choroid plexus. a) First stage; hyperplasia of epithelium of villi (chick T-75). Hematoxylin and eosin. 100 ×; b) the same. 200 ×; c) first stage; mainly connective-tissue response (chick T-13). Hematoxylin and eosin. 100 ×; d) the same. 400 ×; e) second stage; marked epithelial proliferation on villi and penetration through basement membrane (chick T-127). Stained with orcein. 100 ×; f) the same. 400 ×.

syringe through the scalp and cranium into the brain, beneath the meninges or subtentorially.

The chicks were distributed in groups of 506 birds in netting cages, where food and water were replenished daily, and they were inspected twice a day: at the beginning and end of the working day.

Chicks in the agonal state were anesthetized with ether, autopsied, decapitated, and their heads were placed in an acid or neutral 10% solution of formalin (chicks which died underwent the same procedure). After fixation for 6-10 days the head was freed from the cranial bones, taken through alcohols of increasing strength, and embeddeded in paraffin wax. Sections 4-5 μ thick were cut from the wax blocks and stained with hematoxylin and eosin, by the methods of Nissl, Van Gieson, Snesarev, Foot, and Mallory, and with orcein.

EXPERIMENTAL RESULTS

Tumors of the CNS were induced in 12 experiments on 142 chicks aged 1 and 2 days. Of the 142 chicks 54 were of the White Leghorn breed (Enney cross 51 and pure line 3) and 88 chicks were noninbred. Of these numbers 18 chicks of the cross breed, 3 pure White Leghorn, and 13 noninbred chicks were used in the control experiments. The results of these experiments are given in Table 1.

Most of the tumors were meningiomas: 82 of the 108 chicks had meningiomas of the cerebral hemispheres and cerebellum. The second place was occupied by various pathological states of the choroid plexuses of the brain. Changes in the choroid plexuses were observed in the overwhelming majority of cases in the experimental chicks, and in only 3 cases in the control. A rather higher frequency of diseases of the choroid plexuses was observed in noninbred chicks: in 6 of 33 Enney cross chicks (15.1%) and in 16 of 75 noninbred chicks (21.3%).

Three stages of disease of the choroid plexus were distinguished (Table 1).

The initial stage was characterized by a comparatively mild degree of involvement of the choroid plexus, thickening of the walls and loosening of the fibers forming the argyrophilic

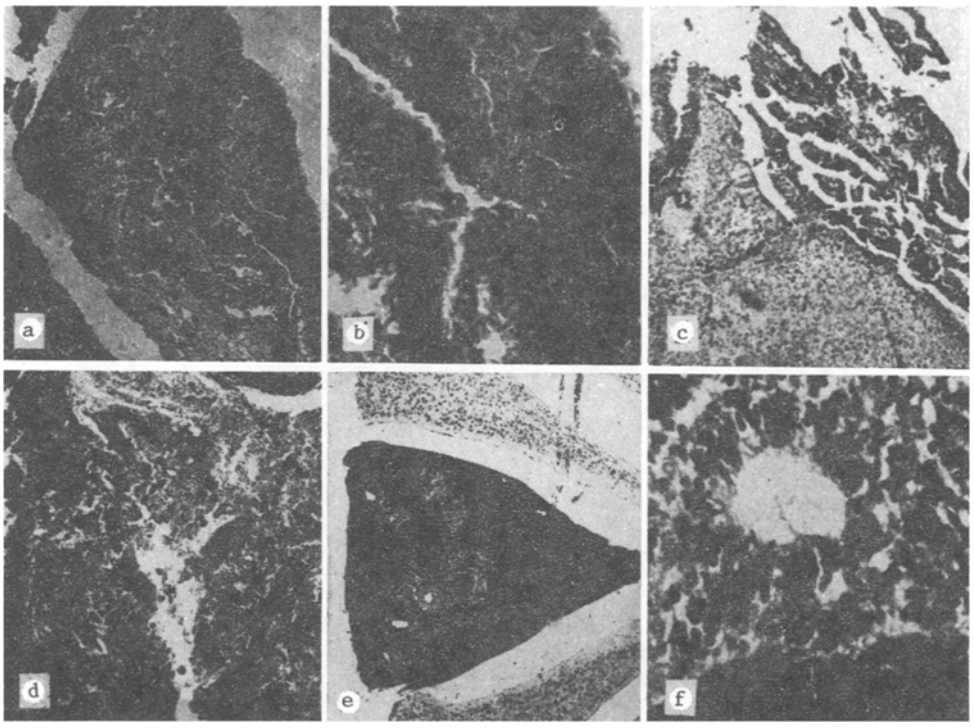

Fig. 2. Third stage of development of tumors of the choroid plexus: atypical tumor growth. a) Adrenocarcinomatous growth of choroid plexus with infiltration of brain tissue (chick No. T-84). Hematoxylin and eosin. 100 ×; b) the same. 400 ×; c) atypical growth of villi (chick T-8). Hematoxylin and eosin. 35 ×; d) the same under higher power. 200 ×; deep invasion of brain tissue by tumor — a malignant choroid epithelioma; e) atypical growth of choroid plexus on account of connective-tissue and epithelial cells with complete loss of structure of the organ (chick T-83). Hematoxylin and eosin. 35 ×; f) the same. 400 ×; mutual infiltration of malignant atypical connective-tissue and epitheloid cells.

framework of the vessels, thickening of the collagen fibers, porosity of the vessel walls with the escaping of blood cells from the vessels, rupture of the vessel walls, and proliferation of the endothelium and perithelium of the vessels. Besides these processes, changes were observed in the epithelial layer covering the villi. From cylindrical and epithelium became cubical in shape. Often the cells were rounded, their arrangement in a single layer was disturbed, and they piled up irregularly to form 3 or 4 rows. Areas such as these gave the villi a curious appearance. At this stage, however, neither hyperchromatosis nor atypia of the cells or the villi themselves could be seen.

The second stage of the choroid epithelioma was characterized by the further growth of atypia of the organ itself and of its cells. At this stage of the disease an increase in the number of altered villi could be seen. Thickened vessels were more numerous. Vascular cells, especially endothelial, became fusiform, with elongated nuclei, and hyperchromic. The lumen of the vessel was filled with atypical polymorphic cells. The boundaries of the vessels disappeared in places. Shapeless piles of dark cells of the polyblast and atypical lymphocyte type were seen. The epithelium of the villi became either cubical or round in shape, it underwent marked proliferation, and became stratified in structure. In some places it penetrated through the basal membranes to reach the proliferating connective-tissue cells arising from the vessels, mingled with them, or invaded them in the form of tongue-shaped masses. The picture described above is evidently the beginning of malignant transformation of a chick choroid epithelioma (Fig. 1).

The third stage of the choroid epithelioma was characterized by atypia of both organ and cells, and by intense hyperchromatosis of the connective-tissue cells. The cells of the tumor of the choroid plexus acquired the capacity for invasive growth, including infiltration of brain tissue (Fig. 2).

Spontaneous diseases of the choroid plexus in man are very rare. In a series of 2023 brain tumors, for instance, Cushing found diseases of the choroid plexus in only 12 cases (0.6%). According to statistics quoted by the majority of authors diseases of the choroid plexus are observed more often in people from 11 months to 29 years of age.

In 50% of cases the lesions were located in the fourth ventricle, in 34.7% in the lateral ventricles, and in 17.3% in the third ventricle. In various animals, according to figures given by the Belaya Tserkov' Agricultural Institute, at 1739 autopsies, including on a total of 1284 calves, pigs, and lambs, and 319 birds, not a single case of diseases of the choroid plexuses was found.

The results completely rule out any possibility of the appearance of spontaneous diseases in the chicks in these experiments. In a table published by the Japanese researcher Ikuta, summarizing the results of intercerebral injection of various viruses into different animals until 1972, only three cases of diseases connected with the cerebral ventricles were mentioned. In one case [12] SV-40 induced ependymomas in newborn hamsters. In the other two cases [9] tumors were obtained in hamsters with the same virus, and in yet another case [14] hyperplastic and papillomatous growths were obtained after intramuscular injection of SV-40. These data are in agreement with the results of the present experiments, for in the control after intravenous injection of AMV we also obtained three tumors of the choroid plexus, and quite a large number of them after intracerebral injection. Consequently, we now know two viruses (SV-40 and AMV) which can induce tumors of the choroid plexus. The problem of the etiological factors in tumors of the choroid plexus and meninges has not hitherto been discussed in the literature. The dominant view that leukomogenic viruses exhibit tropism only for hemopoietic organs, in which they give rise to diseases, must be revised. Our experiments with AMV demonstrated the presence of a broad spectrum of tissues, including tissues of the CNS, that are susceptible to the oncogenic action of the virus. The meninges of the cerebrum and cerebellum, the connective-tissue and epithelial cells of the choroid plexuses, ependymal cells and, finally, nerve tissue cells themselves, are particularly susceptible to it.

The results are evidence in support of the viral etiology of tumors of the choroid plexus of the brain.

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