PRIMATOLOGY

Amyloidosis in Macaques in Adler Primatological Center

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Results of pathomorphological studies of 133 amyloidosis cases in macaques of 3 species (*M. mulatta*, *M. nemestrina*, and *M. fascicularis*) in the Adler Primatological Center are presented. A relationship between the development of amyloidosis and animal age is detected and the incidence of involvement of various organs is determined. Generalized and isolated forms of amyloidosis are described, the most incident of which (36.8%) was hepatic amyloidosis. Simian and human amyloidosis are compared. Amyloidosis in macaques can be used as the model process for studies of amyloidosis in humans.

Key Words: *spontaneous amyloidosis; macaques*

Amyloidosis is a prevalent disease of humans and many animals, which remains a pressing medical problem because of its increasing incidence in countries with well-developed economy. The cause of tissue dysproteinosis with deposit of abnormal fibrillar proteins with different chemical composition is not quite clear. Amyloidosis is traditionally studied on mice, guinea pigs, rabbits, and ducks. In monkeys amyloidosis was considered to be a rare disease till the middle of the 1970s: 5 cases of primary amyloidosis were observed by that time, mainly in baboons, and 15 cases of secondary amyloidosis mainly in macaques. The first descriptions of multiple cases of generalized amyloidosis in monkeys included secondary amyloidosis associated with Yersinia infection [7], chronic colitis and arthritis [2,3,7], retroperitoneal fibromatosis and acquired immunodeficiency syndrome, lymphomas [6,9]. Isolated amyloidosis of pancreatic islets in *M. fascicularis* and *M. mauris* [9,12] is used as a model system for studies of diabetes in elderly humans. Amyloidosis in old rhesus macaques can serve as a model of senile amyloidosis [10]; it is characterized by visceral and brain involvement (amyloid plaques and amyloid angiopathy). Generalized, isolated, familial, and endocrine forms of amyloidosis were not once observed in macaques, red monkeys, and baboons in the Sukhumi Primatological Center [1]. Starting from 1992 amyloidosis is constantly detected in macaques in the Adler Center. This report describes the morphological features of this process.

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MATERIALS AND METHODS

The prevalence and patterns of amyloidosis in macaques living in the Adler Primatological Center were studied on the basis of pathomorphological findings (2588 autopsies). All monkeys were born in the Center or spent there at least 3 years after they were brought from places of their natural habitation.

Each monkey was autopsied using common methods. Organ fragments for histological analysis were fixed in 10% neutral formalin, dehydrated, and embedded in paraffin. The sections were stained with hematoxylin and eosin and selectively with Congo red. The type of amyloid protein was determined by indirect enzyme immunoassay using monoclonal antibodies to fragments of immunoglobulin light chains (κ and λ) in the amyloid deposits in primary amyloidosis [4]. For electron microscopy fragments of organs were fixed in 2% glutaraldehyde solution in phosphate buffer and postfixed in 1% osmium tetroxide. After de-

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hydration in acetone the material was embedded in epon-812. Ultrathin sections were contrasted with lead citrate by the method of Reynolds and examined under a JEM 100B electron microscope.

RESULTS

Amyloidosis was detected in 5.1% of 2588 autopsied macaques in 3 species of the genus. The disease was the most incident in *M. mulatta* (8.1%), less so (6%) in *M. nemestrina*, and rarely (1.3%) in *M. fascicularis*. The disease was not detected in animals aged under 1 year and was regularly diagnosed in animals aged over 8 years (Table 1). Amyloidosis was observed in more than 37.7% animals aged over 20 years. The incidence of amyloidosis was 3.2% in males and 6.2% in females.

Isolated amyloidosis was detected in 88 monkeys (66.2%): with the involvement of the liver in 36.8% of all cases, spleen in 15.8%, kidneys in 6%, lymph nodes in 3.8%, intestine in 2.2%, adrenals and pancreas 0.8% each. Amyloidosis of two and more organs in different combinations was detected in 45 (33.8%) cases. The most incident was simultaneous involvement of the liver, spleen, and intestine (12.8% of all cases), spleen and intestine (7%) or liver, kidneys, and spleen (3.6%). Generalized amyloidosis with involvement of the liver, spleen, kidneys, intestine, and adrenals was observed in 10.4% cases. The liver and spleen were involved most often in all species of monkeys. The intestine ranked third by the frequency of involvement in *M. mulatta* and *M. nemestrina* and the kidneys ranked third in *M. fascicularis*. No generalized disease was detected in any of *M. nemestrina*. The spleen was most often involved in young animals (aged under 8 years), while liver involvement predominated in the rest age groups. Amyloid deposits in the kidneys were not detected in animals aged 9-12 years, but amyloidosis of the intestine was more incident in them than in other age groups.

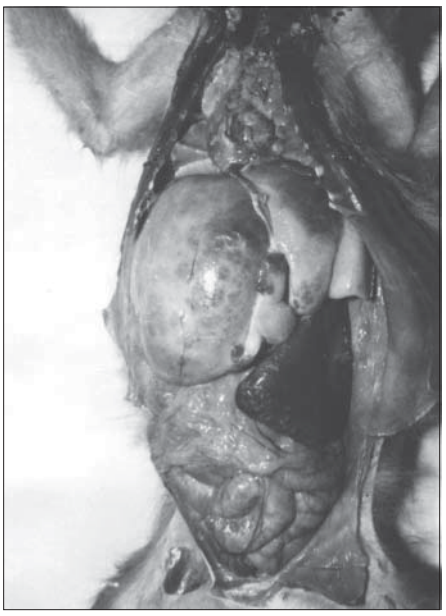

Fig. 1. Sharp enlargement of the liver and spleen in *M. mulatta* with amyloidosis.

Amyloid deposits were often detected during macroscopic examination. The liver was enlarged, sometimes its lower edge reached the umbilical area (Fig. 1) and even the pubis. Its pale-brown tissue acquired a wax-like shade. Thinned strained capsule was easily torn if touched. Enlarged spleen looked "sago" (Fig. 1), rarely "greasy". Kidneys were enlarged in 20% cases and had a tuberous surface and greasy luster on section.

Histological analysis showed homogenous mass selectively stained with Congo red in the walls of central veins of the liver, interlobular arteries and veins. Amyloid did not give typical color reactions in about one-third of animals. Amyloid deposits in the Disse spaces were observed in more manifest process; some-

TABLE 1. Prevalence of Amyloidosis in Different Age Groups of Macaques

Age group	M. mulatta		M. fascicularis		*M. nemestrina*		Total	
	total, including with A*	%	total, including with A	%	total, including with A	%	total, including with A	%
Under 1 year	358/—	—	410/—	—	111/—	—	879/—	—
1-4 years	286/9	3.2	271/1	0.3	49/—	—	606/10	0.2
5-8 years	264/22	8.8	146/3	2.2	32/3	9.4	442/28	6.7
9-12 years	154/24	16.5	76/—	—	29/4	13.8	259/28	11.5
13-16 years	101/20	21.5	77/3	4.0	13/2	15.4	191/25	13.9
17-20 years	62/13	23.2	62/3	5.2	20/3	15.0	144/19	14.2
Over 20 years	39/15	44.1	17/4	23.5	11/4	40.0	67/23	37.7

Note. A*: number of monkeys with amyloidosis in this age group.

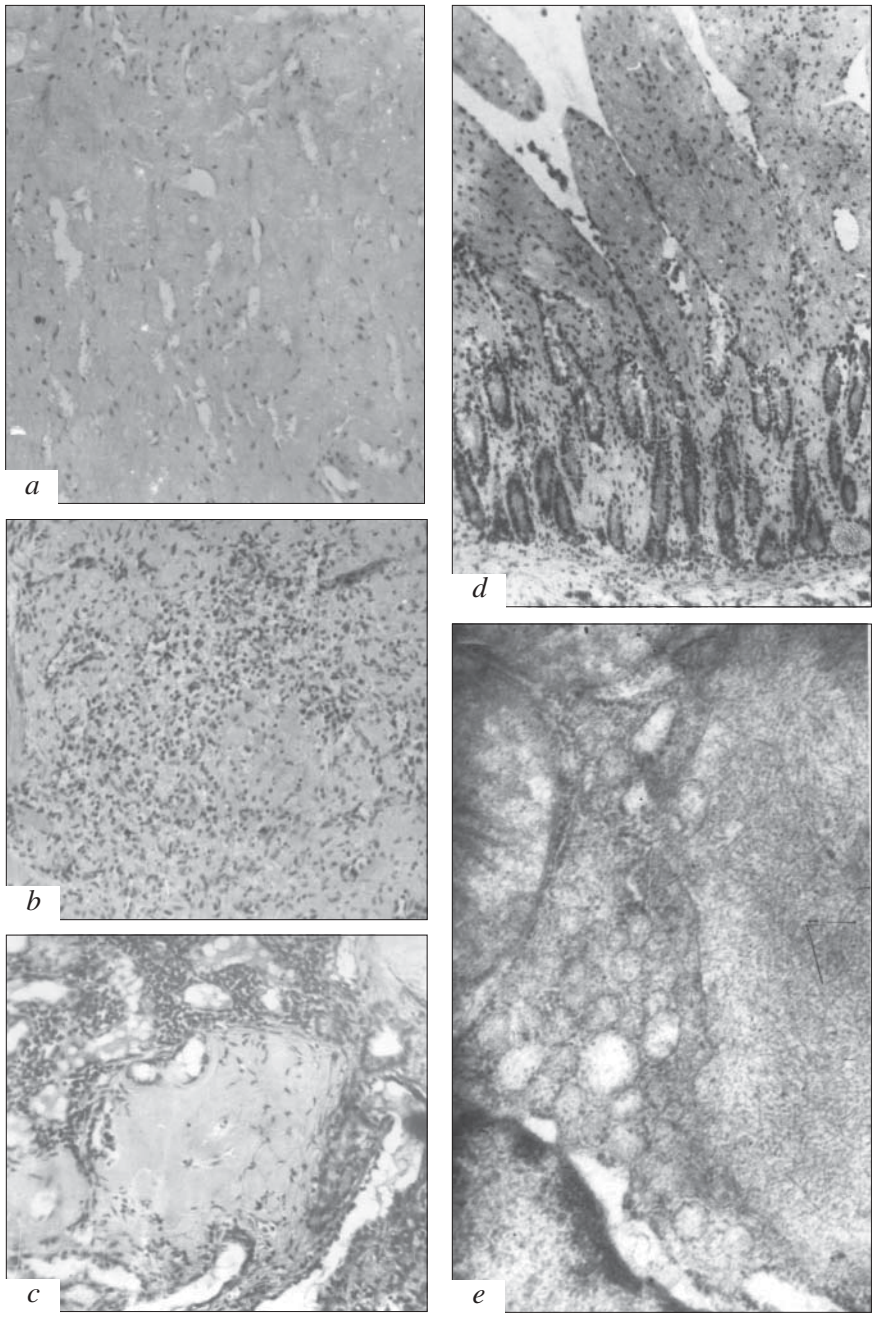

Fig. 2. Organ involvement in macaques with amyloidosis. *a*) massive deposits of amyloid in the liver of *M. mulatta*, Congo red staining, ×40; *b*) diffuse amyloidosis of the spleen in *M. nemestrina*, hematoxylin and eosin staining, ×40; *c*) amyloid in renal vessels and medullary stroma in *M. mulatta*, Congo red staining, ×40; *d*) amyloidosis of the small intestinal mucosa in *M. fascicularis*, hematoxylin and eosin staining, ×40; *e*) fine fibrillar substance in cisterns of endoplasmatic reticulum of a stellate endotheliocyte in the liver of *M. mulatta*, electronogram, ×50,000.

times massive deposits totally replaced hepatocytes in the lobules and caused drastic atrophy of the retained hepatic beams (Fig. 2, *a*). Amyloid deposits in the spleen were seen in follicles and vascular walls and sometimes were located diffusely: in follicles, red pulp, and trabecules (Fig. 2, *b*). In the kidneys amyloid was more often seen in the medullary stroma and vascular walls (Fig. 2, *c*), more rarely under tubular basal membranes and in glomeruli. The adrenals were moderately enlarged in 14 monkeys; foci of hemorrhages and amyloid protein deposits were detected in the interface and cortical layers, in vascular and sinus walls. Hemorrhagic enterocolitis with intense hyperemia, edema, and thickening of the mucosa was detected in the intestine of the majority of monkeys. Amyloid deposits were detected in 33% cases in the submucous

layer, vascular walls, and along reticular fibers of the mucous membrane stroma (Fig. 2, *d*).

Enzyme immunoassay showed the absence of fragments of immunoglobulin light chains in amyloid protein.

Electron microscopy showed mitochondrial hypertrophy in the liver reticuloendotheliocytes associated with hypertrophic rough endoplasmatic reticulum, whose swollen cisterns contained fine fibrillar substance (Fig. 2, *e*).

The majority of monkeys (98 of 133) died from pathological processes in the intestine, such as colitis, enterocolitis, sometimes concomitant with helminthiasis (15 cases) and arthritis (7 cases). Eleven monkeys died from purulent bronchopneumonia. In 3 cases amyloidosis of the liver was detected in *M. mulatta* with malignant tumors (cancer of the cervix and corpus uteri, chondrosarcoma of the shin). Amyloidosis was the underlying disease in 9 monkeys died from accidental causes (traumas in 7 and overcooling in 2 monkeys). In these animals the liver was involved most often (in 5 monkeys), the spleen ranked second (2 monkeys), the mesenteric lymph nodes (1 case) and the adrenals (1 case) were also affected. Amyloid deposits were diffuse in only one 28-year-old monkey: they were detected in the liver, kidneys, spleen, and adrenals. Amyloidosis of the liver, rarely in combination with amyloidosis of the spleen, was the only pathological process in 12 animals with asthenia.

The type of amyloid deposits, the absence of immunoglobulin fragments in it, and the presence of deposits most often in animals with inflammatory processes in the gastrointestinal tract, lungs, joints, and with tumors, indicated that it was a secondary process. As a rule, it was parenchymatous perireticular amyloidosis with hepatopathic, hepatolienal, hepatointestinal, and hepatonephrotic variants, similar to those in human secondary amyloidosis. Like in humans, the incidence of the process was higher and its generalization more frequent in older age groups. Amyloidosis in macaques in the Adler Center, like amyloidosis in macaques in the Sukhumi Center, is mainly hepatic amyloidosis, in contrast to amyloidosis of baboons. It is often the only pathological process similar to the idiopathic variants of human AA amyloidosis. Spleen was more often involved than the liver only in young animals. The predominant involvement of the liver could only partly be explained by the generic appurtenance. Predominant involvement of this or that organ was observed in macaques of different species in different Primatological Centers: involvement of the spleen in *M. nemestrina* [9], pancreas in *M. mauris* [8], brain in old *M. mulatta* [10] in the Washington, Oregon, and Wisconsin Primatological Centers of the USA, respectively. This once more validates that amyloidosis, like any other simian disease, is related to certain conditions of breeding, living, feeding, climate, and place of residence, which are different in different Primatological Centers.

The similarity between macaque and human amyloidosis can be used for utilization of this spontaneous disease of monkeys as a model process in studies of the problems in the pathogenesis and therapy of human amyloidosis.

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