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Experimental Kuru in Macaca Nemestrina: New Anatomical Data*

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Summary. In Macaca nemestrina inoculated intracerebrally by a pin-point injection with a strain of kuru Kupenota (2nd passage), the lesions consisted of spongiosis of neuropile with severe astrocytic hyperplasia, located in the grey matter of cerebral hemispheres (cortex, neostriatum). In all cases, the distribution of lesions was asymmetrical, predominating on the side of injection.

These results suggest that kuru agent could be replicate around the injection site, but the influence of the host and/or the strain could not be excluded.

Key words: Cerebral lesions – Experimental kuru – Macaca nemestrina – Asymmetry – Focal inoculation

Introduction

Previous studies of experimental kuru in the primate showed that, whatever the species of subhuman primate, the strain of the agent and the route of inoculation, cerebral lesions were remarkably stereotyped, bilateral and symmetrical (Beck and Daniel 1979).

We report here an experiment performed in Macaca nemestrina with a strain of kuru (Kupenota) which provides some new neuropathological data.

Material and Methods

Six Macaca nemestrina were inoculated in December 1978 with a strain of kuru (Kupenota MNE 429) passaged intracerebrally one time through Macaca nemestrina, in Dr. Gajdusek and Gibb's laboratory. Inoculation was performed across a trephine hole in the right frontal lobe with a fine needle (0.4 ml of a 10^{-2} dilution of 20% infected brain solution in phosphate buffered saline pH 7.4).

All animals were chronically implanted for EEG recording between December 1979 and February 1980. During this surgical operation the scar of the trephine hole was located in relation to skull sutures. The electrodes were screwed into the cranial bone up to the lamina interna without breaking dura mater and placed symmetrically on both cerebral hemispheres.

Behavioural and neurological studies were performed on the monkeys during the evolution of the disease (Toga et al. 1982).

Animals were killed under general anaesthesia (pentobarbital) at the terminal stage of the disease (29–35 months after inoculation). The skull dome was cut off, the dura mater was opened and the relationship of skull trephine mark to cerebral sulci was made.

Brains were immersion-fixed in 10% formol saline, trimmed coronally at several standard levels and paraffin-embedded. Sections were stained by Loyez's and Bodian's methods, haematoxylin and eosin, and Nissl stain. Healthy animals were examined as controls.

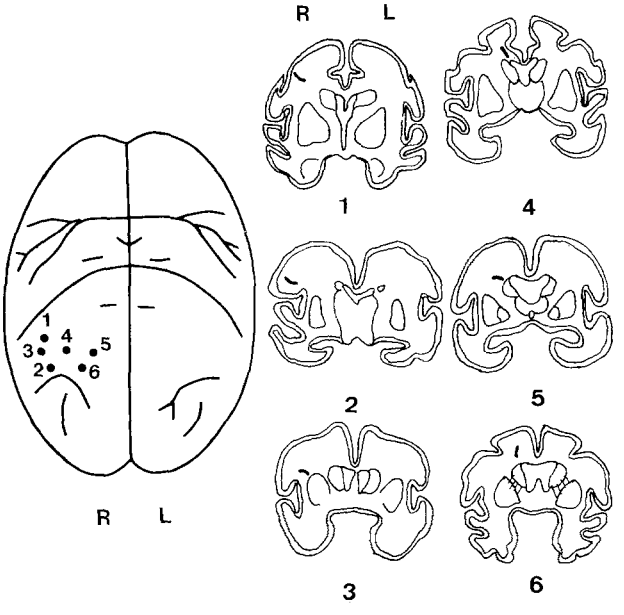

Fig. 1. Localization of the inoculation scars on a superior view and on coronal slices (cases 1–6)

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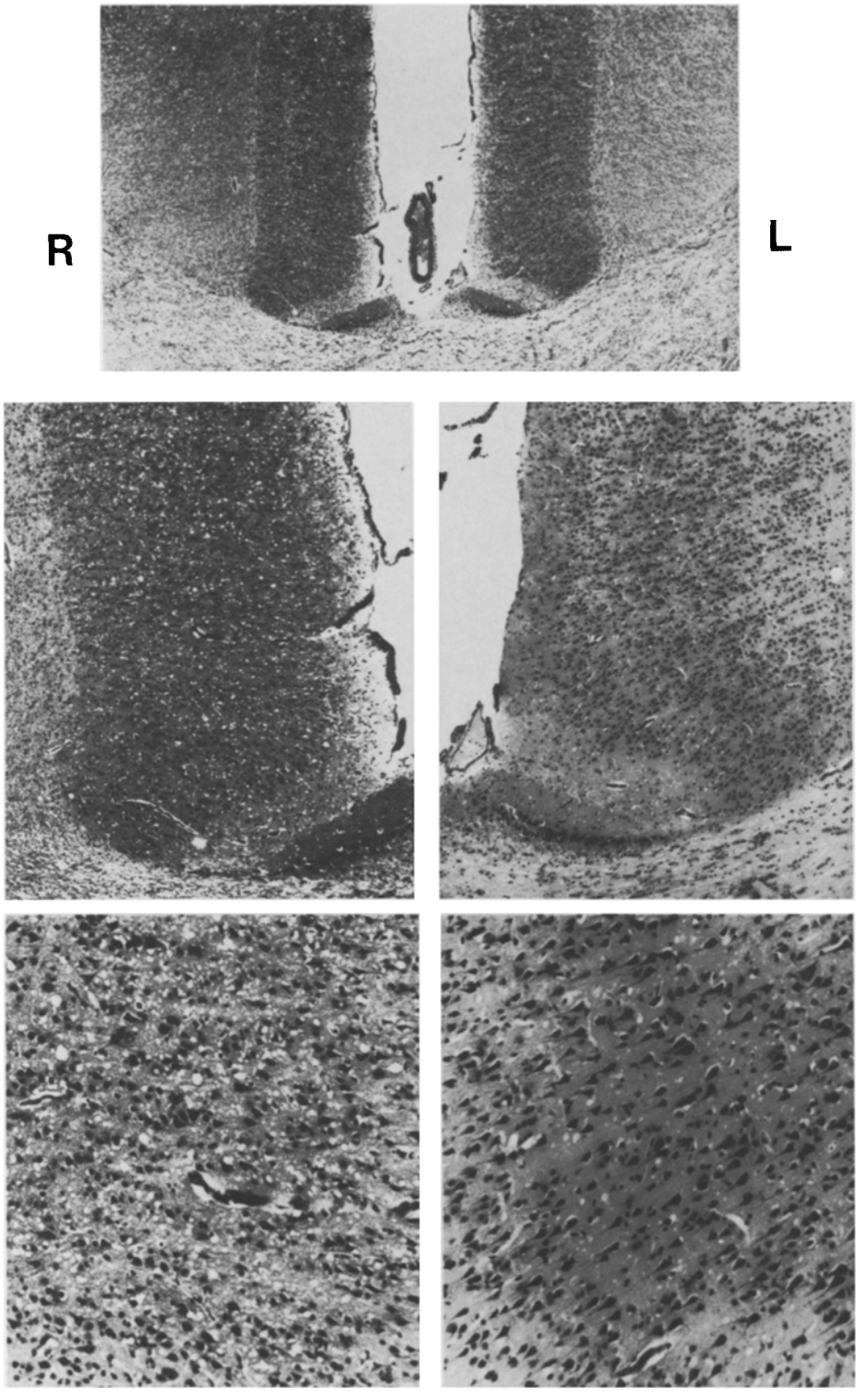

Fig. 2. Asymmetry of lesions in supracallosal gyri (R = right, L = left). From top to bottom: $\times 23$, $\times 60$, $\times 140$

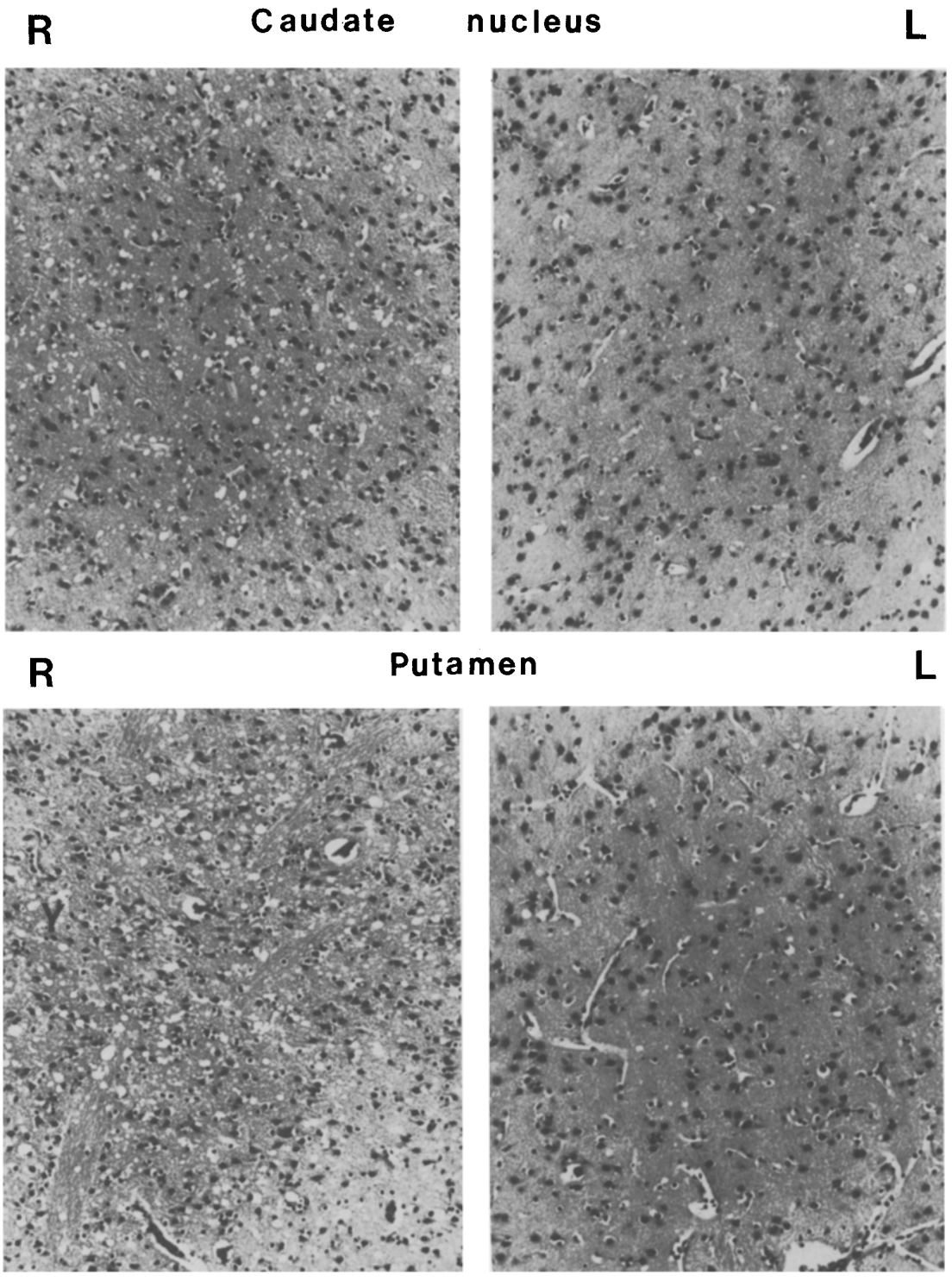

Fig. 3. Predominance of lesions on the right side in caudate nucleus and putamen. × 170

Results

In all our animals, inoculation holes were located behind the right arcuate sulcus (Fig. 1). On coronal brain sections, the injection channel was constantly seen in the subcortical white matter, near the right neostriatum, without break in the lateral ventricle. Individual variations (case 1 to 6) occurred with regard to anteriority and laterality.

The anatomical lesions consisted of spongiosis of the neuropile with neuronal vacuolization and astrocytic hyperplasia occasionally severe in some areas.

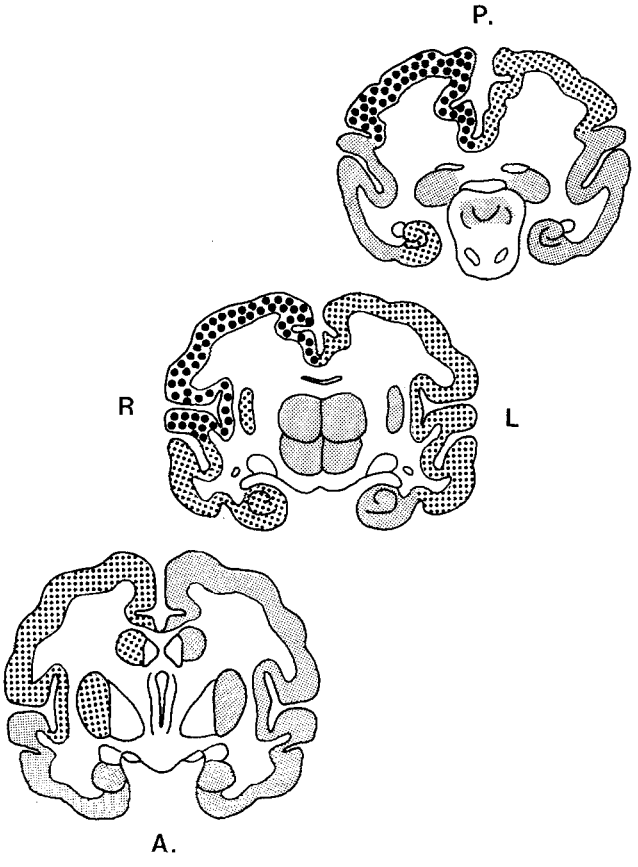

Fig. 4. Asymmetry of lesions on coronal sections from anterior (*A.*) to posterior (*P.*) levels (*R* = right, *L* = left)

Neuronal depopulation was always slight. Lesions were greater in grey matter, involving the cerebral cortex and the neostriatum. They were less important in the thalamus, the subthalamic nuclei, the cerebellum and the brain stem. Lesions were diffuse but more important in some structures of the right cerebral hemisphere (inoculation side) resulting in asymmetrical lesions (Figs. 2 and 3). Whatever the inoculation path, the lesions predominated in the cortical grey matter (frontal and parietal cortex, hippocampus) and the neostriatum (Fig. 4). In some monkeys asymmetry was noted in the thalamus (cases 1 and 2) and substancia nigra (cases 1 and 5). In cerebral cortex, lesions were generally more severe in posterior coronal sections, at thalamus level (Fig. 4). In cerebellum, they were absent or minimal and in this case symmetrical. In five animals, the locus coeruleus showed a slight spongiosis with moderate astrocytic hyperplasia.

Discussion

In Macaca nemestrina injected intracerebrally with a strain of kuru Kupenota brain lesions were essentially represented by spongy vacuolation of the neuropile accompanied by astrocytic hyperplasia. These changes were similar to those seen in the experimental kuru of the rhesus monkey inoculated with the strain Enage L6 56 (Gambarelli et al. 1981), but in Macaca nemestrina, astrocytic hyperplasia was often more severe, especially in the cerebral cortex. We did not find the neuronal loss described in the human kuru (Klatzo et al. 1959; Beck et al. 1969) and in the experimental kuru of other primates (Beck et al. 1973, 1975; Peterson et al. 1973; Cathala et al. 1975). Brain lesions affected essentially the cortical mantle and the neostriatum; the cerebellar involvement was very slight contrasting with that described in the human kuru (Beck et al. 1969) and in the experimental kuru of chimpanzee (Beck et al. 1973) and spider monkey (Lampert et al. 1969; Masters et al. 1976; Beck and Daniel 1979). This shifting of lesions from cerebellum to cerebral cortex and basal ganglia had also been reported in experimental kuru of rhesus monkey (Gambarelli et al. 1981).

The most striking feature in our cases was the brain distribution of lesions which were constantly more intense in the inoculated cerebral hemisphere. This asymmetry had never been reported in human kuru as well as in experimental kuru of primate. It could not be the consequence of the implantation of the EEG recording device since in kuru of rhesus monkey, we have not found asymmetrical changes in animals implanted with the same experimental procedure. Another possibility is that asymmetry result from the use of a different strain of the kuru agent (Kupenota MNE 429 strain): indeed, Bruce and Dickinson (1979) with some scrapie strains produced in mice asymmetrical brain lesions. However, in kuru of primate, central nervous system changes were always symmetrical, whatever the strain (Beck et al. 1970, 1975; Cathala et al. 1975). Asymmetry may also be related to the use of another species of Macaca, i.e. Macaca nemestrina. These facts have been demonstrated for scrapie by Bruce et al. (1976) and Fraser (1982). Finally, the distribution of lesions might depend on route of infection: in our animals, the intracerebral pin-point injection was always performed in the same area into the subcortical white matter. At the time of inoculation, the inoculum could not diffuse either into the cerebrospinal fluid or in the blood as it was probably the case in kuru of rhesus monkey where we used both intracerebral and intravenous routes. With scrapie agent, Bruce and Fraser (1981) have shown that, in mouse brain, the frequency and distribution of amyloid plaques depended on the route of intracerebral injection and that frequency of plaques was higher on the side of injection. Fraser (1982) described vacuolar changes confined to the contralateral superior colliculus in mice injected intraocularly with scrapie and suggested a neuronal spreading of this agent.

Moreover, Bruce and Fraser (1982) reported focal and asymmetrical spongy vacuolation in mice intracerebrally inoculated. Their interpretation was that scrapie infectivity did not spread evenly throughout the brain but remained in the region of needle track and replicated there.

So, like scrapie, Kupenota kuru agent could first replicate around the injection site and later diffuse into the nervous system by neuronal spread, the lesions remaining more severe around the inoculated area. To confirm this hypothesis, further experimental work with kuru agent is needed in the primate.

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References

Beck E, Bak IJ, Christ JJ, Gajdusek DC, Gibbs CJ, Hassler R (1975) Experimental kuru in the spider monkey. Histopathological and ultrastructural studies of the brain during early stages of incubation. Brain 98:595–612

Beck E, Daniel PM (1979) Kuru and Creutzfeldt-Jakob disease: neuropathological lesions and their significance. In: Prusiner SB, Hadlow WJ (eds) Slow transmissible diseases of the nervous system, vol 1. Academic Press, New York, pp 253–270

Beck E, Daniel PM, Alpers M, Gajdusek DC, Gibbs CJ (1969) Neuropathological comparison of experimental Kuru in chimpanzees with human Kuru. In: Burdzy K, Kallos P (eds) Pathogenesis and etiology of demyelinating diseases (Add ad.). J Int Arch Allergy 36:553–562

Beck E, Daniel PM, Asher DM, Gajdusek DC, Gibbs CJ (1973) Experimental Kuru in the chimpanzee. A neuropathological study. Brain 96:441–462

Beck E, Daniel PM, Gajdusek DC, Gibbs CJ (1970) Subacute degenerations of the brain transmissible to experimental animals: a neuropathological evaluation. Proceedings of 6th Congress of Neuropathology. Masson, Paris, pp 858–873

Bruce ME, Dickinson AG (1979) Biological stability of different classes of scrapie agent. In: Prusiner SB, Hadlow WJ (eds) Slow transmissible diseases of the nervous system, vol 2. Academic Press, New York, pp 71–86

Bruce ME, Dickinson AG, Fraser H (1976) Cerebral amyloidosis in scrapie in the mouse: effect of agent strain and mouse genotype. Neuropathol Appl Neurobiol 2:471–478

Bruce ME, Fraser H (1981) Effect of route of the injection on the frequency and distribution of cerebral amyloid plaques in scrapie mice. Neuropathol Appl Neurobiol 7:289–298

Bruce ME, Fraser H (1982) Focal and asymmetrical vacuolar lesions in the brains of mice infected with certain strains of scrapie. Acta Neuropathol (Berl) 58:133–140

Cathala F, Court L, Hauw JJ, Escourolle R, Rohmer F, Castaigne P (1975) Clinical studies in primates inoculated with kuru and Creutzfeldt-Jakob agents. Adv Neurol 10:319–339

Fraser H (1982) Neuronal spread of scrapie agent and targeting of lesions within the retino-tectal pathway. Nature 295:149–150

Gambarelli D, Vuillon-Cacciuttolo G, Toga M, Bert J (1981) Anatomical study of experimental kuru in rhesus monkey. Acta Neuropathol (Berl) 53:337–341

Klatzo I, Gajdusek DC, Zigas V (1959) Pathology of Kuru. Lab Invest 8:799–847

Lampert PW, Earle KM, Gibbs CJ, Gajdusek DC (1969) Experimental kuru encephalopathy in chimpanzees and spider monkeys. J Neuropathol Exp Neurol 28:353–370

Masters CL, Kakulas BA, Alpers M, Gajdusek DC, Gibbs CJ (1976) Preclinical lesions and their progression in the experimental spongiform encephalopathies (kuru and Creutzfeld-Jakob disease) in primates. J Neuropathol Exp Neurol 35:593–605

Peterson DA, Wolfe LG, Deinhardt F, Gajdusek DC, Gibbs CJ (1973–1974) Transmission of Kuru and Creutzfeldt-Jakob disease to marmoset monkeys. In: Melnick JL (ed) Intervirology. Karger, Basel, pp 14–19

Toga M, Michel B, Gambarelli D, Vuillon-Cacciuttolo G, Balzamo E, Bert J (1982) Approches anatomo-cliniques dans les maladies expérimentales à virus non conventionnels (kuru et Creutzfeldt-Jacob) chez le macaque. Communication au symposium "Virus non conventionnels et affections du système nerveus central", Paris, 5–7 novembre 1981 (in press)

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