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EXPERIMENTAL ENCEPHALITOZOONOSIS IN THE BLUE FOX

CLINICAL, SEROLOGICAL AND PATHOLOGICAL EXAMINATIONS OF VIXENS AFTER ORAL AND INTRAUTERINE INOCULATION

By

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MOHN, S. F., K. NORDSTOGA and I. W. DISHINGTON: *Experimental encephalitozoonosis in the blue fox — Clinical, serological and pathological examinations of vixens after oral and intrauterine inoculation.* Acta vet. scand. 1982, *23*, 490—502. — Inoculations of vixens with Encephalitozoon cuniculi (E. cuniculi), performed orally, either before or in the gestation period, or directly into the uterus at oestrus, induced clinical encephalitozoonosis in the offspring. The infection of the vixens, indicated by a general E. cuniculi antibody response, appeared to run a subclinical course. Endometritis was detected in some of the vixens when examined at the end of the trial. A temporary increase of total protein, albumin and globulin in the inoculated vixens compared to the controls was detected in the final 2 weeks of the gestation, concomitantly with the rise in humoral E. cuniculi antibody titres. The antibody levels appeared significantly higher in the group of vixens inoculated directly into the uterus than in the orally inoculated groups. Vixens exposed to the parasite seemed to possess a certain degree of acquired resistance to re-infection with the parasite when exposed in the following breeding season.

blue fox vixens; encephalitozoonosis; clinical signs; serology; pathology.

Encephalitozoonosis is a world-wide protozoan infection of homeothermic animals (*Wilson* 1979). The disease is caused by Encephalitozoon cuniculi (E. cuniculi), which is an exclusively intracellular parasite classified within the family Glugeidae of the order Microsporida. Encephalitozoonosis is best known in laboratory rodents, where the infection is usually inapparent

or runs a mild course. In the rabbit the infection is generally accepted to be transmitted horizontally, almost invariably via the oral route. Evidence of vertical transmission has, however, been reported in a few cases (*Hunt et al.* 1972, *Owen & Gannon* 1980). The natural mode of infection in other mammalian species is largely unknown, although vertical transmission has been reported in experimental studies with mice (*Perrin* 1943) and in a few spontaneous cases in the squirrel monkey (Saimiri sciureus) (*Anver et al.* 1972, *Brown et al.* 1973).

During the last decade encephalitozoonosis has occasionally caused serious losses among young blue foxes (Alopex lagopus) in Norway (*Nordstoga* 1972, *Nordstoga et al.* 1974, *Nordstoga & Westbye* 1976). Vertical transmission via placenta has been suggested to be the likely mode of infection (*Mohn et al.* 1974), and the disease may be experimentally induced by injecting the parasite directly into the uterus of vixens (*Nordstoga et al.* 1978). Recent trials have provided evidence for transplacental transmission of the parasite after oral inoculation of the dams (*Mohn et al.* 1974, *Mohn et al.* 1982), and it seems that foetuses have to be infected in utero before clinical encephalitozoonosis in the young pups can be induced (*Mohn & Nordstoga* 1982). Dams of pups affected by encephalitozoonosis have always appeared to be clinically healthy, and parasites and/or pathological lesions have never been detected in the organs of adult foxes from farms where encephalitozoonosis has been widely distributed among the pups (*Mohn et al.* 1974).

The aim of the present paper is to report the results obtained by clinical, serological and pathological investigations of vixens after oral and intrauterine inoculations of the parasite at various junctures in the gestation period. In order to study the ability of the vixens to resist re-infection of the parasite, an oral- re-inoculation trial was conducted during the following breeding season.

MATERIALS AND METHODS

Organism

A strain of E. cuniculi previously isolated from a blue fox that died from natural encephalitozoonosis was propagated in monolayer cell cultures, as described elsewhere (*Mohn et al.* 1981).

Inoculations

Doses of about 4×10^5 spores harvested from the cell culture medium were injected intraperitoneally into Swiss albino mice of the outbread stock Bom:NMRI f(SPF). After 12—16 days some of the mice were killed and cut into pieces and fed to healthy vixens, as described elsewhere (*Mohn et al.* 1982). From the other inoculated mice peritoneal exudate, containing spores of E. cuniculi mainly located intracytoplasmically in macrophages, was collected, and doses of 2 ml exudate were injected directly into the uterus of the vixens. The inoculations were carried out according to an insemination technique described by *Fougner et al.* (1973) within 24 h after the second natural mating.

Vixens

Primary inoculation trial

Twelve E. cuniculi sero-negative vixens about 10 months old, and 12 adult sero-negative vixens 2—4 years old, which had given birth to normal pups in the previous season, were selected at random to form an experimental and a control group, each group comprising 12 vixens. The experimental group was subdivided into 3 subgroups, each comprising 2 young and 2 adult vixens.

Subgroup 1. Each vixen was fed 3 E. cuniculi-infected mice 38—58 days before mating.

Subgroup 2. Each vixen received mouse peritoneal exudate by intrauterine injections, as described above.

Subgroup 3. Each vixen was fed 3 infected mice on day 20 after the first mating day.

Control group. The foxes remained untreated.

The mean mating day (MMD) of the vixens was calculated as the mean of the first mating day of each vixen in the 2 groups.

Re-inoculation trial

The following breeding season, within a period of from 12 days before to 6 days after mating, 1 vixen from each of the subgroups 1 and 2, and 2 vixens from subgroup 3 were re-inoculated orally by being fed with E. cuniculi-infected mice, as

described above. Two vixens from subgroup 1 and 1 vixen from each of subgroups 2 and 3 remained untreated.

All vixens were kept in wire mesh cages; the control and the experimental groups in separate sheds. They were fed at regular intervals with the same food as the non-experimental animals and treated as the other vixens in the farm, including 2 matings with intervals of 2 days.

Clinical examinations

Physical observations. The vixens were examined at weekly intervals in conjunction with collection of blood samples.

Haematology. The examinations were carried out on freshly collected venous blood with the addition of 2.5 % of an anticoagulant, consisting of disodiumethylenediaminetetraacetate (EDTA) and formaldehyde at final concentrations of approximately 10 % in sterile destilled water. Haemoglobin was measured photometrically at 540 nm by the Haemiglobin cyanide method (Dade HICN-Reagent, Merz + Dade AG, 3018 Berne, Switzerland). Packed cell volume (PCV) was determined in capillary tubes run for 6 min in a Cellokrit centrifuge (AB Lars Ljungberg & Co, Stockholm, Sweden). Determination of total white cell count was done by an electronic particle counting device (Celloscope 401, Lars Ljungberg & Co, Stockholm, Sweden).

Biochemistry. The analyses were performed on sera separated from venous blood samples. Total protein was measured by the biuret method (*Weichselbaum* 1946). Albumin was determined by the bromcrezol green method (*Doumas et al.* 1971), and globulin was calculated by subtracting the albumin from the total protein values. Urea was measured by a full-enzymatic method described by *Talke & Schubert* 1965). Aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) were determined at 37°C, as described by *Keiding et al.* (1974). All analyses were performed in a Gemsaec fast analyzer.

Serological examinations

The tests were carried out on sera separated from venous blood samples. The sera were tested for antibodies to E. cuniculi by the india-ink immunoreaction (IIR) modified by *Kellett & Bywater* (1978). The titres were expressed as the reciprocal

value of the highest serum dilution showing more than 5 % spores stained with carbon particles of at least 200 spores examined.

Post-mortem examinations

Four vixens from each trial were euthanized at the normal time for pelting and necropsied according to routine schedules. Sections of cerebrum, myocardium, kidneys, uterus and ovaries were stained with haematoxylin and eosin (HE), elastin van Gieson and with a modified Gram method (*Petri* 1969).

Statistical calculations

The statistical tests on results of the haematological and biochemical analyses were performed by using Student's t-test.

RESULTS

Primary inoculation trial

Clinical examinations. The pregnant vixens delivered after a gestation peroid of normal length. The number of pups and results of the clinical observations of the vixens and their

Table 1. Clinical and serological examinations of vixens and offspring in the experimental and in the control group of the primary inoculation trial.

Group	Sub-group No.	Vixens Nos.	Number of vixens exhibiting clinical signs of disease	Number of vixens developing E. cuniculi antibodies	Number of pregnant vixens	Number of litters in each group	Number of pups in each litter	Number of pups in each litter exhibiting signs of clinical encephalitozoonosis[1]
Experimental	1	1—4	0	4	3	3	9, 12, 12	9, 10, 12
	2	5—8	0	4	2	1	13	11
	3	9—12	0	4	4	2	3,4	0,1
Control	—	13—24	0	0	12	10	2, 2, 5, 7, 9, 10, 10, 10, 10, 11	0[2]

[1] Clinical signs of weakness, reduced growth, blindness and neurological disturbances (ataxia, lameness, circling behaviour, convulsions).

[2] 0: None of the pups in the 10 litters suffered from clinical encephalitozoonosis.

Table 2. Haematological and biochemical analyses of samples collected from the vixens in the experimental and in the control group at 3 various stages during the primary inoculation trial; mean values ± s.

Parameter	Days after mean mating day (MMD) 1 Experimental[1] group	1 Control group	1 P[2]	41 Experimental[1] group	41 Control group	41 P	76 Experimental[1] group	76 Control group	76 P
Total leukocyte count 1000/µl blood	5.7± 1.4	6.7± 1.5	—[3]	8.0± 2.0	9.0± 1.8	—	10.8± 3.1	9.8± 3.7	—
Haemoglobin g/100 ml blood	17.8± 1.2	17.0± 1.0	—	15.1± 1.9	14.1± 1.2	—	14.4± 2.0	14.6± 2.3	—
PCV % of blood	52 ± 5	53 ± 4	—	46 ± 5	43 ± 4	—	44 ± 8	44 ± 7	—
Total protein g/l serum	64 ± 3	65 ± 2	—	66 ± 5	57 ± 4	0.0005	72 ± 5	71 ± 8	—
Albumin g/l serum	41 ± 2	43 ± 2	—	33 ± 3	30 ± 3	0.01	36 ± 3	36 ± 4	—
Globulin g/l serum	23 ± 2	22 ± 3	—	33 ± 4	27 ± 6	0.01	36 ± 5	35 ± 5	—
Albumin/ Globulin ratio	1.8± 0.2	2.0± 0.4	—	1.0± 0.2	1.1± 0.5	—	1.0± 0.2	1.0± 0.2	—
ASAT U/l serum	51 ±11	55 ±14	—	50 ±25	41 ±18	—	68 ±33	91 ±24	—
ALAT U/l serum	98 ±45	76 ±21	—	76 ±43	55 ±23	—	126 ±62	83 ±29	—
Urea mmol/l serum	4.8± 1.6	5.6± 1.1	—	6.6± 1.3	8.2± 1.8	—	8.6± 4.2	10.4± 3.7	—

[1] Subgroups 1, 2 and 3 combined.
[2] P: Significance of difference between the means of the experimental and the control group.
[3] —: $P > 0.05$.

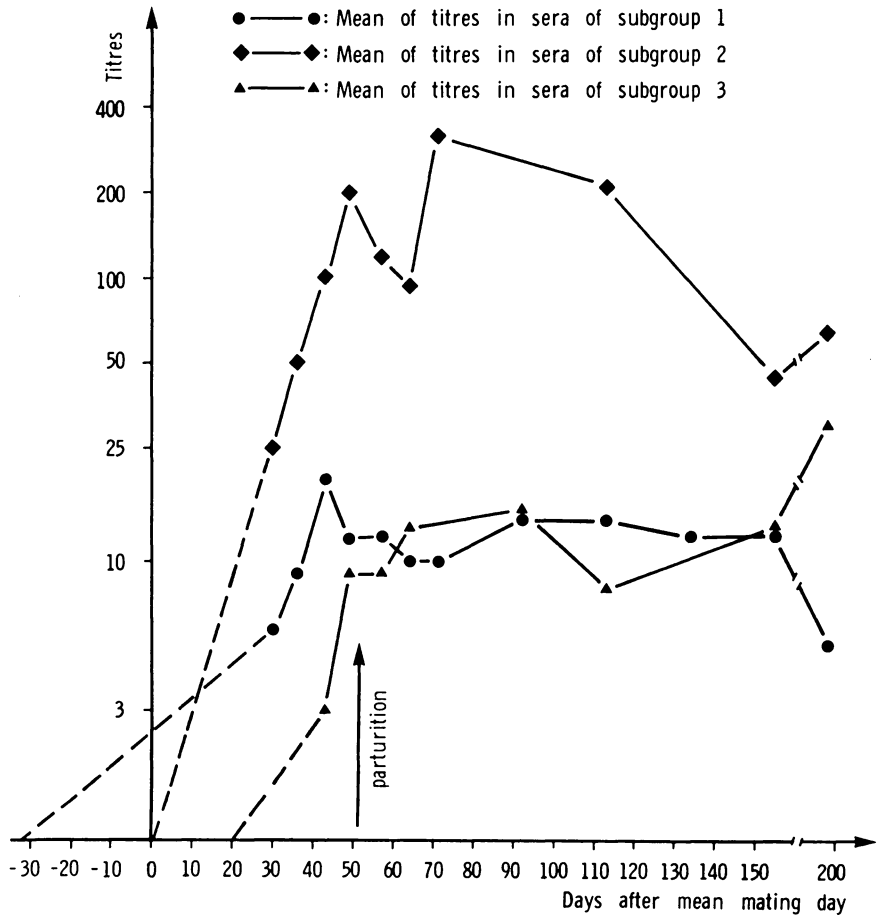
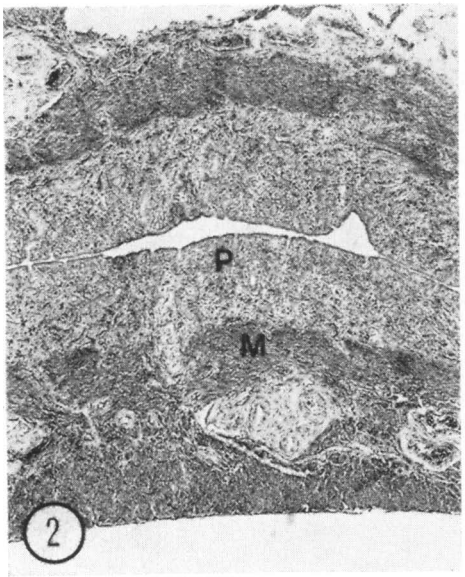
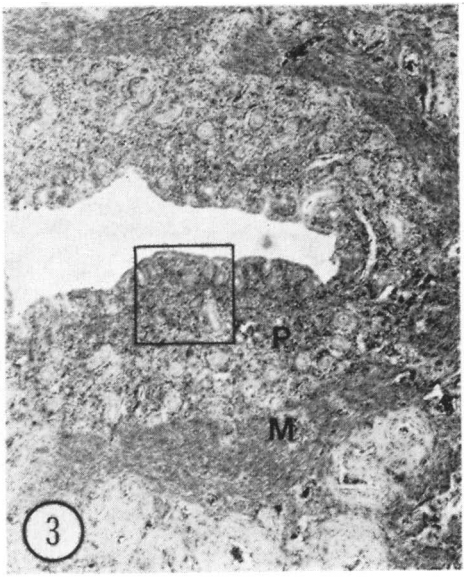


Figure 1. E. cuniculi antibody titres in sera sampled from the vixens in the experimental subgroup 1 (orally inoculated 32 days before mating), subgroup 2 (inoculated in utero at mating), and in subgroup 3 (orally inoculated 20 days after mating).

offspring are shown in Table 1. The results of the haematological and biochemical examinations obtained in samples from the vixens of the experimental and the control group, collected 32 days before and 1, 22, 41, 76 and 102 days after MMD, were compared statistically. The result of the samples collected 1, 41 and 76 days after MMD are presented in Table 2. No significant differences were found between the 2 groups in samples obtained at the various other junctures not presented in the table. Excepted from this was the significantly higher ($P < 0.05$) concen-





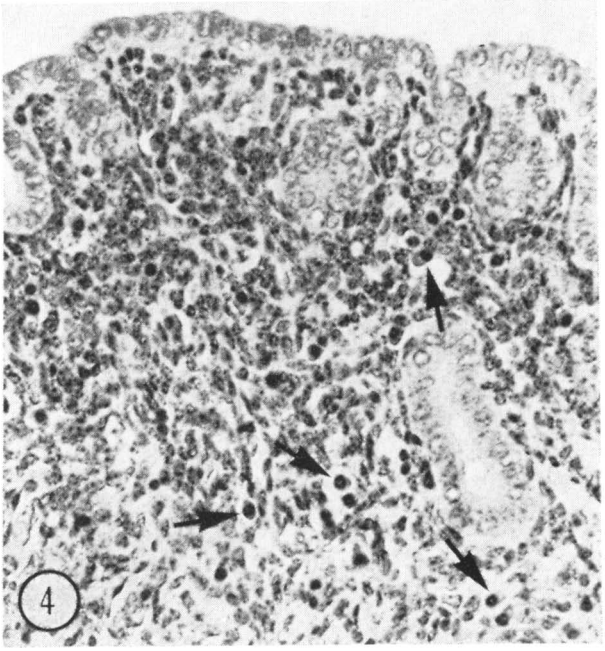


Figure 2. Normal uterine wall of a control vixen. P = lamina propria. M = inner muscular layer. HE, × 63.

Figure 3. Uterine wall of vixen inoculated with E. cuniculi spores. Lamina propria is thickened and infiltrated by inflammatory cells. P = lamina propria. M = inner muscular layer. HE, × 63.

Figure 4. Detail of the framed area of Fig. 3 showing infiltration of inflammatory cells in lamina propria, predominantly mononuclear inflammatory cells, some of which appear to be plasma cells (arrows). HE, × 390.

tration of urea in the experimental group (11.1 ± 2.7 mmol/l) than in the control group (8.9 ± 2.4 mmol/l) 102 days after MMD. Statistical comparisons of experimental subgroups 1—3 with the control group 41 days after MMD showed a significant increase of the total protein in all subgroups ($P < 0.01$, 0.0005 and 0.001, respectively). Globulin was found significantly elevated in subgroup 2 ($P < 0.025$), whereas albumin was significantly increased in subgroup 3 only ($P < 0.005$).

Serological examinations. The results are presented in Fig. 1 and in Table 3.

Table 3. Serological, pathological and clinical examinations of vixens and offspring in the re-inoculation trial.

Group	Vixen Nos.	E. cuniculi antibody titres in the vixens prior to re-inoculation	E. cuniculi antibody titres in the vixens at pelting time	Specific pathological lesions in organs of the vixens	Number of pups delivered	Number of pups developing clinical encephalito-zoonosis
Re-inoculated	2	<10	<10	0[2]	13	0
	5	10	25	+[3]	12	2
	11	<10	<10	—[4]	7	0
	12	25	25	0	10	0
Non-treated	1	<10	—[1]	0		
	3	<10	<10	—	16	0
	6	50	25	—	0	0
	9	<10	<10	0	9	0

[1] Died 27 days after the second mating.
[2] 0: No pathological lesions detected.
[3] +: Thickened lamina propria of the endometrium with infiltrations predominantly of mononuclear inflammatory cells, including some plasma cells (Figs. 3 and 4).
[4] —: Necropsy not performed.

Pathological examinations. One vixen from each of subgroups 1 and 3 and 2 vixens from subgroup 2 were killed and necropsied. No macroscopic or histological lesions were detected in the organs, except that the lamina propria of the uterine walls from all vixens appeared thickened, compared to the controls, and infiltrated predominantly by mononuclear inflammatory cells, including some plasma cells (Figs. 2—4).

Re-inoculation trial

The results are shown in Table 3. The sero-positive vixens showed titres at low levels during the trial; a maximum titre of 100 was found in vixen No. 6. The vixens without detectable antibodies prior to re-inoculation remained sero-positive up to the time of pelting, except for vixen No. 2 which revealed a titre of 25 on day 79 post whelping. Uterine lesions in vixen No. 5 were similar to those in the vixens of the primary inoculation trial (Figs. 3—4).

DISCUSSION

The various modes of primary inoculation of vixens resulted in clinical encephalitozoonosis of the offspring (Table 1). The results do not show with any apparent significance whether one of the modes was superior to the other in transferring the agent to the offspring, although 31 out of the 33 pups in subgroup 1 developed the disease. In subgroup 2, one litter only survived the perinatal stage. This finding could indicate that direct inoculation into the uterus of the vixens resulted in a more serious infection of the foetus than oral inoculation, causing foetal death or abortions, or pups born weak that died shortly after delivery. All vixens within the experimental group developed E. cuniculi antibodies (Table 1). In subgroups 1 and 2 the antibodies appeared before the time of whelping, whereas the vixens in subgroup 3 became sero-positive later in the course of the trial (Fig. 1). These findings seem to correspond with previous results which showed a period of 30—35 days after infection before the IIR was able to detect antibodies (*Mohn* 1982). The antibody levels of subgroups 1 and 2 decreased towards the end of the trial, while a certain rise was found from about 155 days after MMD in subgroup 3 (Fig. 1). This increase was due to the late appearance of antibodies in the dam of the litter that failed to develop clinical encephalitozoonosis (Table 1). This vixen seemed to have escaped the infection after the primary oral inoculation, and in contrast to the other inoculated vixens, was infected after whelping, most likely through transmission of the parasite from clinically diseased pups kept in the same shed. Its pups became sero-positive to E. cuniculi from the age of 43 days, which may indicate a neonatally acquired infection through routes similar to those through which the mother was infected (*Mohn & Nord-*

stoga 1982). The significantly higher antibody response in subgroup 2 than in the others (Fig. 1) could indicate that parasites inoculated directly into the uterus were allowed more favourable conditions for multiplication, probably with haematogenous spreading to other organs, than parasites inoculated orally into the dams. The inoculated vixens did not show clinical signs of disease (Tables 1 and 3). These findings correspond with previous observations in natural outbreaks of fox encephalitozoonosis (*Mohn et al.* 1974). The vixens necropsied after the primary inoculation trial all had inflammatory lesions in the uterine wall, however, without detectable parasitic structures. Transmission trials have provided evidence for intrauterine infection of the offspring via placenta (*Mohn et al.* 1982), and the uterus appears to be a predilection site for the parasite in the vixen. It seems therefore probable that the endometritis may have been caused by heavy doses of the E. cuniculi spores inoculated through various routes into the vixens, although participation of other infectious agents cannot be excluded. Similar lesions in the endometrium are possibly also present in natural cases of the disease; the prevalence is, however, unknown, since no systematic histological examination on the uterus has been performed. The results of the laboratory tests (Table 2), which appeared to be within the range of results obtained from a normal blue fox population (*Berestov* 1971), confirm the general concept of a subclinical course of infection in the vixens. The significantly higher concentrations of total protein, albumin and globulin in the experimental group than in the controls, detected 41 days after MMD (Table 2), and appearing concomitantly with the rise in circulating E. cuniculi antibodies (Fig. 1), could probably reflect the parasite infection. An extensive hypergammaglobulinaemia, as seen in clinically affected pups (*Mohn & Nordstoga* 1975), was not, however, observed in the inoculated vixens.

Five out of the 8 sero-positive vixens selected for the re-inoculation trial were found sero-negative when tested primo March, prior to re-inoculation (Table 3). This finding corresponds with previous observations (*Mohn & Nordstoga* 1975, *Mohn*, unpublished) and shows the ability of the blue fox to overcome the infection. Vixen No. 5 in the re-inoculation trial was primarily inoculated in utero, and its antibody titre indicated that it was still harbouring the parasite at the time of re-

inoculation. Whether the establishment of clinical encephalitozoonosis in some of its pups was due to a latent infection, possibly in the uterus as indicated by the inflammatory reactions seen in the endometrium, rather than to the re-inoculated parasites, cannot be ascertained. The occurrence of inflammatory lesions in the endometrium (Figs. 3 and 4) of this particular vixen, compared to the normal conditions in the uterus of the mothers of the healthy litters in this trial (Fig. 2 and Table 3), also indicate that the endometritis is correlated to the E. cuniculi infection. The failure to produce clinical encephalitozoonosis in the offspring of the other vixens in this trial, in contrast to the high morbidity rate in litters of primary inoculated vixens without any history of previous exposure to E. cuniculi (Table 1, *Mohn et al.* 1982, *Mohn & Nordstoga* 1982), seems, however, to show that the exposed vixens, even without possessing detectable humoral antibodies at the time of re-inoculation, resist re-infection. The development of clinical encephalitozoonosis in litters of the same dam at 2 subsequent breeding seasons has occasionally been observed in natural cases of the disease (*Mohn*, unpublished). Although such cases appear to be rare, it is recommended that dams of clinically diseased pups, as well as all seropositive reagents within an affected farm (*Mohn & Nordstoga* 1982), be destroyed in order to control the disease.

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SAMMENDRAG

Eksperimentell encephalitozoonose hos blårev — Kliniske, serologiske og patologiske undersøkelser av tisper etter oral og intrauterin podning.

Podning av blårevtisper med Encephalitozoon cuniculi (E. cuniculi) enten oralt før eller under drektigheten eller direkte i uterus i forbindelse med brunsten, fremkalte klinisk encephalitozoonose hos avkommet. Tispene svarte på podningen med dannelse av humorale E. cuniculi-antistoffer, men infeksjonen syntes å ha et subklinisk forløp. I tispene som ble pelset, ble det i endometriet påvist fortykket lamina propria med infiltrasjon vesentlig av mononukleære betennelsesceller, inkludert en del plasmaceller. Et forbigående forhøyet innhold av totalprotein, albumin og globulin i de podete tispene i forhold til kontrollene ble påvist i de 2 siste uker av drektighetsperioden. Denne tilstanden ble registrert samtidig med en økning i påvisbare sirkulerende E. cuniculi-antistoffer. Gruppen av intrauterint podete tisper utviklet signifikant større mengder antistoffer enn de oralt podete tispene. Tisper tidligere smittet med E. cuniculi så ut til å ha en viss forøket resistens mot reinfeksjon med parasitten.

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