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EXPERIMENTAL ENCEPHALITOZOONOSIS IN THE BLUE FOX

CLINICAL AND SEROLOGICAL EXAMINATIONS OF AFFECTED PUPS

By

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MOHN, S. F.: *Experimental encephalitozoonosis in the blue fox — Clinical and serological examinations of affected pups.* Acta vet. scand. 1982, *23*, 503—514. — Two groups of blue fox pups about 1½—2 and 2½—3 months old, respectively, suffering from experimental encephalitozoonosis, were examined clinically and serologically. Antibodies to Encephalitozoon cuniculi were detected in all pups, the titres varying within the range 10—12,800. In addition to unspecific signs of disease the pups showed various neurological disturbances including ataxia, posterior weakness, lameness and circling behaviour, terminating in recumbency, paralysis or convulsions. Reduced sight or blindness was observed occasionally. Some of the pups appeared thirsty. Haematological examinations revealed pronounced leukocytosis without any conspicuous shift within the various groups of leukocytes. Biochemical examinations of serum showed significant elevated values of urea nitrogen, creatinine, and magnesium concentrations, reflecting renal dysfunction. Alanine aminotransferase was found significantly depressed in both groups. Raised levels of total protein were demonstrated due to pronounced hyperglobulinaemia. This finding, together with the common occurrence of generalized polyarteritis nodosa and proliferations of plasma cells in clinically affected pups, is probably a result of autoimmune disturbances initiated directly or indirectly by the protozoan infection.

blue fox pups; encephalitozoonosis; clinical signs; serology.

Encephalitozoonosis is an infectious protozoan disease reported from a variety of mammalian species and birds (*Wilson* 1979). The infection is caused by Encephalitozoon cuniculi (E. cuniculi), which is an exclusively intracellular parasite classified within the family Glugeidae of the order Microsporida (*Canning* 1977). The infection is commonly detected in the domestic rab-

bit, where it usually is inapparent or runs a mild course (*Shadduck & Pakes* 1971). Parasites that have been shown to be morphologically identical with E. cuniculi and closely antigenically related to strains isolated from the rabbit (*Mohn et al.* 1981, *Mohn* 1982) are occasionally found to infect the blue fox (Alopex lagopus), causing serious losses among the pups (*Nordstoga* 1972, *Nordstoga et al.* 1974). Vertical transmission via placenta has been suggested to be the likely mode of infection, and recent experiments have indicated transplacental transmission of the parasite after oral inoculations of the dams (*Mohn et al.* 1974, *Mohn et al.* 1982b). Prenatal infection of the foetus appears to be essential for the development of clinical disease with characteristic signs, since pups inoculated neonatally have run an almost subclinical course of infection without developing the severe pathological lesions occurring in the clinically affected pups (*Mohn & Nordstoga* 1982). The concept of a subclinical course of infection in the dams of naturally affected pups has been confirmed by serological, haematological and biochemical examinations of inoculated vixens, whereas the occurrence of endometritis in some of these dams has indicated that the uterus may be a predilection site for the infection in the adult fox (*Mohn et al.* 1982a).

A variety of clinical signs exhibited by the affected pups have been described in natural and experimental cases (*Nordstoga* 1972, *Nordstoga et al.* 1974, *Mohn & Nordstoga* 1982). Examinations of serum proteins in naturally diseased pups have shown a marked hyperproteinaemia due to hypergammaglobulinaemia (*Mohn & Nordstoga* 1975). The present paper is a contribution to the knowledge of the clinical manifestation of fox encephalitozoonosis, with special reference to haematological, serological and relevant biochemical examinations related to the pathological lesions accompanying fox encephalitozoonosis.

MATERIALS AND METHODS

Pups

A f f e c t e d g r o u p. Twelve pups 43—64 days old and 27 pups 72—99 days old borne by vixens orally inoculated by E. cuniculi spores (*Mohn et al.* 1982a) and exhibiting clinical signs of disease were selected for clinical and serological examinations.

Healthy group. Eight pups 43—64 days old and 27 pups 72—99 days old borne by non-inoculated clinically normal vixens, without any signs of disease, were selected for clinical and serological examinations.

Examination methods

Physical observations. The clinical signs of disease shown by the individuals were observed and dates of deaths recorded.

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 distilled 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). Blood films were prepared on slides, air-dried, and fixed in methanol for 5 min. The preparations were stained with May-Grünewald-Giemsa, and differential counting of the leukocytes was performed with a 100 × immersion oil objective.

Biochemistry. The analyses were carried out 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). The analyses mentioned above were performed in a Gemsaec fast analyzer. Creatinine was assayed photometrically at 490 nm (Heinz Haury Chemische Fabrik, München, West-Germany). Calcium (Ca), magnesium (Mg), sodium (Na) and potassium (K) were detected by atomic absorption (Perkin-Elmer 303).

Serology. The sera were tested for antibodies to E. cuniculi by the modified india-ink immunoreaction (*Kellett & Bywater* 1978), originally described by *Waller* (1977). 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.

Statistical calculations

The statistical tests on the results of the analyses were performed with the use of Student's t-test.

RESULTS

The pups in the experimental group exhibited a variety of clinical signs. Most of the pups appeared depressed and weak, being in bad condition and showing reduced appetite and a rough hair coat. Abnormal thirst was occasionally observed. Some of the pups were dull, whereas others appeared to be restless. In more advanced cases various signs of neurological disturbances including ataxia, posterior weakness, lameness of one or more legs, and circling behaviour with tilted heads, were commonly seen. Recumbency, paralysis, and convulsions occurred frequently in the terminal stage of the disease. Reduced sight or blindness due to cataract was seen in some of the pups, especially in the group 72—99 days old. The mortality rate within the experimental group was calculated to 74 %, most of the pups dying during their first 2—4 months of life. The affected pups reaching the normal time of pelting appeared small in size (3.4 ± 0.7 kg body weight) with rough hair coat consisting mainly of wool with few deck hairs. The pups in the normal groups remained healthy throughout the observation period, revealing body weights of 6.7 ± 0.7 kg at pelting.

The results of the haematological examinations are presented in Table 1, and the results of the biochemical and serological examinations are shown in Table 2.

DISCUSSION

The clinical signs of disease observed in the pups of the affected groups are in accordance with the findings previously reported in natural and experimental cases of fox encephalitozoonosis (*Nordstoga* 1972, *Nordstoga et al.* 1974, *Mohn & Nord-*

Table 1. Haematological findings in the groups of pups suffering from clinical encephalitozoonosis compared to the findings in the healthy groups.

Parameter	Age of the pups (days)					
	43—64			72—99		
	Affected group mean ± s (n[1]=12)	Healthy group mean ± s (n=8)	P[2]	Affected group mean ± s (n=26)	Healthy group mean ± s (n=27)	P
Haemoglobin g/100 ml blood	11.8± 0.9	11.5± 0.4	—[3]	12.5± 1.7	13.1± 0.7	0.05
PCV % of blood	36 ± 3	36 ± 2	—	38 ± 6	40 ± 2	—
Total leukocyte count 1000/µl blood	14.7± 4.0	10.3± 2.6	0.001	18.3± 8.8	11.6± 4.4	0.001
Eosinophils %	0.2± 0.3	0.5± 0.8	—	1.0± 1.0	2.7± 2.0	0.0005
Juvenile neutrophils %	1.2± 1.4	1.5± 0.9	—	1.1± 0.9	1.3± 1.2	—
Neutrophils - rod-shaped nucleus %	0.6± 0.6	1.5± 1.1	0.025	0.7± 0.6	0.4± 0.5	0.05
Neutrophils- segmented nucleus %	46.0±13.8	38.1±10.5	—	33.1±14.9	32.8± 8.7	—
Lymphocytes %	48.0±15.0	53.4±11.6	—	60.4±15.3	58.8±11.8	—
Monocytes %	4.1± 2.9	5.0± 1.7	—	3.7± 2.1	3.6± 2.6	—

[1] n: Number of pups in each group.
[2] P: Significance of difference between the means of the affected and the healthy group.
[3] —: $P > 0.05$.

stoga 1982). The reduced appetite, weakness, stunting and retarded growth seem to be unspecific signs of the disease, whereas the various neurological disturbances appear to be related to lesions in the central nervous system (*Nordstoga* 1972, *Mohn & Nordstoga* 1982). Some of the pups in the group 43—64 days old showing severe neurological signs died after a relatively short course of the disease. In these cases cerebral haemorrhages, commonly seen at necropsy, were assumed to be the direct cause of death. Unspecific signs were more prominent in the cases with protracted course of the disease. Severe interstitial nephritis, meningo-encephalitis, and polyarteritis nodosa were conspicuous necropsy findings in these cases; renal dysfunction appeared to account for a majority of the deaths in these animals. The high

Table 2. Biochemical and serological findings in serum samples from the groups of pups suffering from clinical encephalitozoonosis compared to the findings in the healthy group.

Parameters	Age of the pups (days) 43—64 Affected group mean ± s (n[1]=9)	43—64 Healthy group mean ± s (n=8)	P[2]	73—99 Affected group mean ± s (n=27)	73—99 Healthy group mean ± s (n=22)	P
Total protein g/l	94 ±14	56 ± 3	0.0005	78 ± 15	55 ± 5	0.0005
Albumin g/l	27 ± 3	35 ± 2	0.0005	33 ± 7	35 ± 3	0.05
Globulin g/l	67 ±12	21 ± 2	0.0005	45 ± 20	20 ± 3	0.0005
Albumin/globulin ratio	0.4 ± 0.1	1.7 ± 0.2	0.0005	0.7 ± 0.5	1.8 ± 0.3	0.0005
ASAT U/l	107 ±27	91 ±16	—[4]	100 ± 74	100 ±38	—
ALAT U/l	49 ±17	103 ±15	0.0005	108 ±120	211 ±93	0.001
Urea mmol/l	17.3 ± 4.4	6.2 ± 1.0	0.0005	14.0 ± 8.0	8.0 ± 1.5	0.001
Creatinine[3] µmol/l				118 ± 17	76 ±15	0.0005
K mmol/l	6.4 ± 0.9	7.3 ± 0.7	0.025	6.0 ± 0.7	5.6 ± 0.8	0.05
Mg mmol/l	1.16± 0.02	1.06± 0.08	—	1.11± 0.22	0.91± 0.10	0.0005
Ca mmol/l	2.9 ± 0.4	3.0 ± 0.2	—	2.8 ± 0.1	2.7 ± 0.3	—
Na mmol/l	145 ± 5	149 ± 4	0.05	149 ± 11	145 ±13	—
E. cuniculi antibody titre (range)	2000±3900 (50—12,800)	<10	0.0005	900±1400 (10—6400)	<10	0.0005

[1] n: Number of pups in each group.
[2] P: Significance of difference between the means of the affected and the healthy group.
[3] : Performed on 8 sera selected from the elder group of affected pups showing urea concentrations ranging from 13.1 to 46.5 mmol/l, and on 6 sera from the healthy group with urea levels ranging from 5.5 to 9.1 mmol/l.
[4] —: $P > 0.05$.

mortality rate, with the majority of deaths occurring within 2—4 months of age, is in accordance with previous observations in experimental cases (*Mohn & Nordstoga* 1982), and in natural outbreaks of the disease (*Nordstoga et al.* 1974). The few affected pups brought for pelting were almost worthless, owing to retarded growth and defective development of the furs.

The slightly reduced values of haemoglobin, combined with packed cell volume within the normal range seen in the affected group of pups 72—99 days old (Table 1), indicate a tendency towards a normocytic hypochromic anaemia, probably due to the chronic infection and renal lesions (*Schalm et al.* 1975). Both groups of affected pups responded to the disease with a significant leukocytosis (Table 1), indicating high reactive capacity to the infection. However, no conspicuous shift within the various types of leukocytes was observed, except that the elder group of affected pups showed eosinopenia (Table 1), which seems to contrast with the reports of eosinophils within normal range in most cases of chronic nephritis in the dog (*Schalm et al.* 1975); the eosinopenia of the diseased pups may probably be related to mechanisms established by the generalized protozoan infection. The total leukocyte count in the healthy groups appeared to be on an elevated level compared to values reported from another normal blue fox population, whereas the differential counts of the leukocytes seemed to be within the same range (*Berestov* 1971).

The raised levels of total protein in the affected groups, due to pronounced hyperglobulinaemia, and combined with a significant hypoalbuminaemia (Table 2), are in accordance with electrophoretic findings showing marked hypergammaglobulinaemia in naturally diseased pups (*Mohn & Nordstoga* 1975). After about 1 month from infection the majority of specific antibodies to E. cuniculi is found within the IgG class of the gammaglobulin fraction (*Waller et al.* 1978, *Mohn* 1982); from a quantitative point of view the elevated gammaglobulin fraction is, however, likely to consist mainly of antibodies to antigenic determinants different from those of the parasite. Circulating complexes of Australia antigen and immunoglobulins have been demonstrated in humans suffering from polyarteritis nodosa, the injured arterial walls of the patients containing complexes of the antigen, IgM, fibrinogen and complement (*Paronetto & Strauss* 1962, *Paronetto* 1969, *Gocke et al.* 1971). Generalized polyarteritis

nodosa and massive plasma cell infiltrations in affected organs, including spleen, lymph nodes, and bone marrow, are common findings in natural and experimental cases of clinical blue fox encephalitozoonosis (*Nordstoga & Westbye* 1976, *Arnesen & Nordstoga* 1977, *Mohn & Nordstoga* 1982). A close relationship may also exist between the pathological lesions and the raised levels of humoral gammaglobulins in the blue fox, probably developing as the result of immune reactions, most likely of the type III hypersensitivity. E. cuniculi infected adult foxes and neonatally inoculated young pups do not seem to develop pathological lesions similar to those occurring in the prenatally infected pups (*Mohn et al.* 1982a, *Mohn & Nordstoga* 1982); prenatal infection of the foetus thus appears to be essential for the development of the possible patho-immunological disturbances in the pups, induced directly or indirectly by the infecting parasite.

The significant difference between the ALAT in the affected and healthy pups of both age groups (Table 2) is difficult to relate to any of the pathological lesions observed in the pups. It is, however, suggested that these findings are due to a general depression of cell activity, the liver included, during the course of the chronic infectious disease. There is a considerable distinction between ALAT values found in the healthy groups and the values (29 ± 15 U/l) in normal blue foxes reported by *Berestov*; the discrepance appears to have resulted mainly from the use of different analysing methods. The significantly raised urea nitrogen in both groups of affected pups combined with elevated creatinine levels (Table 2), is an indication of renal functional failure (*Sodikoff* 1981), and corresponds with the commonly occurring lesions of interstitial nephritis observed in affected pups (*Nordstoga* 1972, *Mohn et al.* 1982b). The concentration of potassium in the serum does not seem to have been substantially affected by the renal dysfunction, since the alterations found are small when compared to the controls, the younger group of affected pups even showing slightly depressed amounts (Table 2). The increased magnesium concentration in the elder group of affected pups (Table 2) is likely to reflect renal disease, with a breakdown in the mechanism of fixing the serum magnesium threshold concentration (*Simesen* 1970). Hypermagnesaemia occurs in connection with renal dysfunctions, usually associated with a drop in serum calcium (*Berestov* 1971); normal calcium

levels were, however, detected in the present groups (Table 2). The slightly lowered concentration of sodium in the younger group of affected pups (Table 2) may be associated with injury of parts of the renal tubuli and disorder of the re-absorption of the element (*Berestov* 1971, *Schalm et al.* 1975).

The serological examinations revealed titres within a wide range (Table 2), the findings being in accordance with previous reports (*Mohn* 1982, *Mohn et al.* 1982b, *Mohn & Nordstoga* 1982). The mean titres appear significantly elevated compared to the mean titres detected in pups neonatally inoculated with E. cuniculi at almost the same stage of infection (*Mohn* 1982). The serological test appears to be a specific method for the diagnosis of experimental encephalitozoonosis, showing complete correlation between positive reactions and clinically diseased pups as well as between negative reactions and healthy pups (Table 2). A positive correlation seems to exist between the antibody titres and the clinical stage of the disease.

In conclusion the clinical and serological findings in experimentally induced encephalitozoonosis seem to correspond with present experience from the naturally occurring disease. The results obtained in this trial may also be taken into consideration in "spontaneous" cases, the laboratory tests being useful tools for confirming the diagnosis in natural outbreaks of the disease.

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SAMMENDRAG

Eksperimentell encephalitozoonose hos blårev — Kliniske og serologiske undersøkelser av syke valper.

To grupper blårevvalper i alderen henholdsvis 1½—2 og 2½—3 måneder, begge med eksperimentelt indusert encephalitozoonose, ble undersøkt klinisk og serologisk. Encephalitozoon cuniculi-antistoffer ble påvist hos alle valpene med titre varierende mellom 10 og 12 800. I tillegg til uspesifikke symptomer viste valpene forskjellige neurologiske forstyrrelser som svakhet i bakparten, ataksi, halthet, dreid hodeholdning, sirkelbevegelser, kramper og lammelser. Nedsatt syn eller blindhet på grunn av katarakt ble påvist i enkelte tilfelle. Noen valper var påfallende tørste. Hematologiske undersøkelser viste en uttalt leukocyttose uten betydelige forskyvninger mellom de enkelte typer leukocytter. Biokjemiske undersøkelser av serum viste signifikant forøket innhold av urea nitrogen, kreatinin og magnesium som tegn på dysfunksjon i nyrene. Begge grupper viste signifikant redusert aktivitet av alanin aminotransferase. Konsentrasjonene av totalprotein

og globulin i serum var betydelig forøket. Det synes å være en nær sammenheng mellom forandringene i immunglobulinene og de vanlig forekommende vevsskader hos klinisk syke valper i form av generalisert polyarteritis nodosa og massive plasmacelleinfiltrasjoner i angrepne organer. Disse forandringene kan være et resultat av autoimmune forstyrrelser hos valpene indusert direkte eller indirekte etter prenatal infeksjon med Encephalitozoon cuniculi.

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