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## CHRONIC RELAPSING EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS IN RATS: CLINICOPATHOLOGICAL COURSE, SOME GENETICAL AND IMMUNOLOGICAL ASPECTS

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**SUMMARY** Experimental allergic encephalomyelitis was induced in rats of various genotypes by active immunization with an encephalitogenic bovine brain extract. Chronic relapsing clinical disease was noted in juvenile F<sub>1</sub> progeny of Albino Oxford males and Dark August females in a high percentage of animals, 65–75% varying from series to series of experiments, and in Dark August strain in only 20–25% of animals. We report here the summary of clinicopathological, genetical and some immunological analyses F<sub>1</sub> rats. Our results confirmed (1) the close similarities in morphology of central nervous system, lesions between chronic relapsing clinical disease and multiple sclerosis, (2) the essential role of cell-mediated immunity in the pathogenesis of experimental allergic encephalomyelitis, (3) the fact that experimental allergic encephalomyelitis susceptibility is a genetic trait, and (4) the existence of a defective systemic immune regulation in chronic relapsing clinical disease.

### INTRODUCTION

Experimental allergic encephalomyelitis (EAE) is a T lymphocyte-mediated autoimmune disease of the central nervous system (CNS) which can be induced in susceptible animals by immunization with

CNS extracts or a myelin basic protein (MBP) administered in an appropriate adjuvant<sup>1</sup>. In the case of chronic relapsing form of the disease (CR-EAE), EAE serves as the best experimental animal model for the pathogenetic study of multiple sclerosis (MS)<sup>2,3</sup>. From the clinico-pathological point of view there are close similarities between the animal and the human

counterpart of demyelinating disorder<sup>3,4</sup>. From the genetical aspect it is well known that susceptibility to EAE varies between different species and strains of laboratory animals. This susceptibility is regulated by major histocompatibility complex (MHC) and probably by non-MHC genes<sup>5,6,7</sup>. Finally, from the immunological aspect the T lymphocyte-mediated immune reaction in EAE is well characterized<sup>8,9</sup> but the role of humoral immune mechanisms still remains hypothetical<sup>10,11,12</sup>. Furthermore, the immunologic evidence of defective immune regulation in CR-EAE<sup>13,14</sup> gives yet another aspect applicable in MS research.

We previously documented a model of CR-EAE in the (AOxDA)F<sub>1</sub> rats<sup>15,16</sup>. Now we describe our investigations in pathohistological changes, genetical aspects and immunoreactivity in this model.

## MATERIALS AND METHODS

The rat strain studied is the (AOxDA)F<sub>1</sub> strain originally obtained from our laboratory. Strains DA, AO and Y-59 were used as comparable groups. The animals were 6–11 weeks old when immunized.

The immunization procedure and the EAE scoring were made as in our previous studies<sup>15,16</sup>. The rats were immunized into the dorsum of both hind feet with 0.1 ml of an encephalitogenic emulsion of bovine brain white matter in complete Freund's adjuvant (CFA). Control animals were nontreated or injected with CFA alone.

Rats were followed up with daily weighing and observation for neurological signs. Clinical signs of EAE were scored on a scale of 0 to 4, where 0 stands for no signs; 1 for flaccid tail; 2 for flaccid tail and hind limb paresis; 3 for paralysis and anaesthesia of the tail and hind limbs plus incontinence; 4 for death.

Animals were sacrificed by decapitation. The brains and spinal cords obtained at different stages of CR-EAE were fixed in formalin and then stained with various methods: hematoxylin and eosin (H-E), Nissl's stain, Fox stain, Sudan III, Giemsa and toluidine blue.

### Immunological analysis

Cellular immunity of specific type was assessed by delayed-type skin sensitivity to bovine brain white matter. Skin tests were performed on a shaved area of the abdomen. The animals were injected intradermally with encephalitogenic material dissolved in 0.1 ml of saline. The diameter of the erythema and induration was measured at 24–48 hours after challenge. Nonspecific cellular immunity was assessed by allogenic skin graft rejection and humoral reactivity by plaque forming cell (PFC) assay.

### Statistical analysis

Data were analysed statistically with Student's t-test.

## RESULTS

### Clinical findings

The clinical course observed in the used strains of rats is summarized in Table 1. Y-59 rats were completely resistant to EAE induction. Rats of AO strain also showed a low rate of incidence also (10% with the acute disease). Conversely, a high degree of susceptibility (100%) was obtained in rats of DA strain with a recurrence of clinical signs in 20–25% of them. Only (AOxDA)F<sub>1</sub> rats developed a chronic relapsing clinical disease in a higher percentage (65–75%). In these rats, after a latent period of eight days after the immunization, the disease was manifested through an acute EAE attack. The acute episode was generally followed by a complete remission of the disease one week after the first neurologic signs. After 22 days about the 70% of animals showed spontaneous relapse with a similar degree of clinical disease severity to that recorder during the initial attack. This stage was followed by a complete remission about one week later. The animals were followed 6 months after the immunization without further evidence of significantly exacerbations.

TABLE 1 Incidence of chronic relapsing experimental allergic encephalomyelitis in various strains of rats

Strain	No.	Acute disease incidence (%)	Incidence of CR-EAE (%)	Clinical disease severity <sup>x</sup>
DA	42	100	20–25 <sup>xx</sup>	2.8
(AOxDA) F <sub>1</sub>	100	100	65–75 <sup>xx</sup>	2.5
AO	31	10	0	0.5
Y-59	25	0	0	0.1

<sup>x</sup>The scoring system for evaluation of the clinical severity of the disease was previously described (Morović et al. 1983)

<sup>xx</sup>Variations from one to another series

### Morphologic findings

Initial attack - during this period CNS lesions consisted mostly of perivascular cuffs of mononuclear cells, polymorphonuclear cells together with oedema and sometimes haemorrhage. Few macrophages and eosinophils were found within perivascular cuffs (Figure 1).

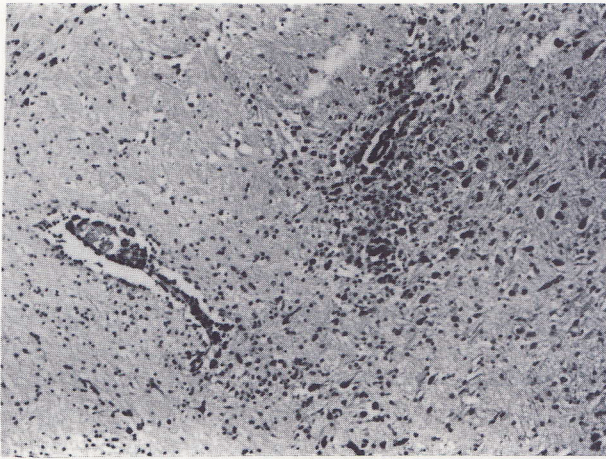


FIGURE 1 Perivascular cuffs in cerebral parenchyma of (AOxDA)F<sub>1</sub> rat, 9 days after immunization; HE; x78.75

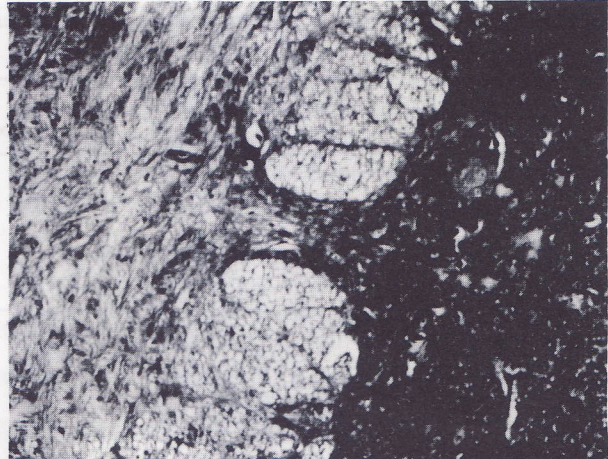


FIGURE 3 Partial demyelination in pontine white matter (transverse pontine fibers) of (AOxDA)F<sub>1</sub> rat; 22 days after immunization

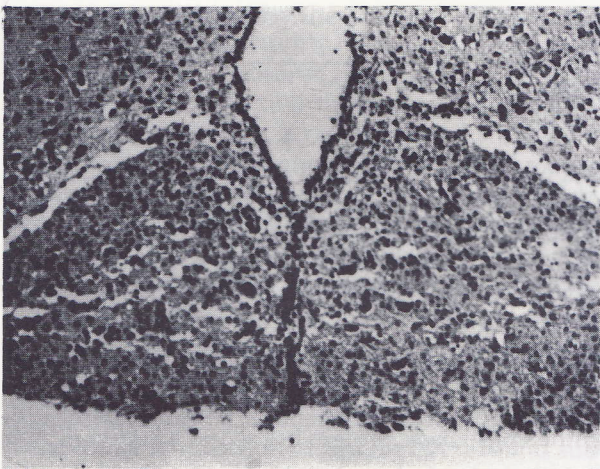


FIGURE 2 Diffuse reactive gliosis in periventricular area of (AOxDA)F<sub>1</sub> rat, 15 days after immunization; HE; x126

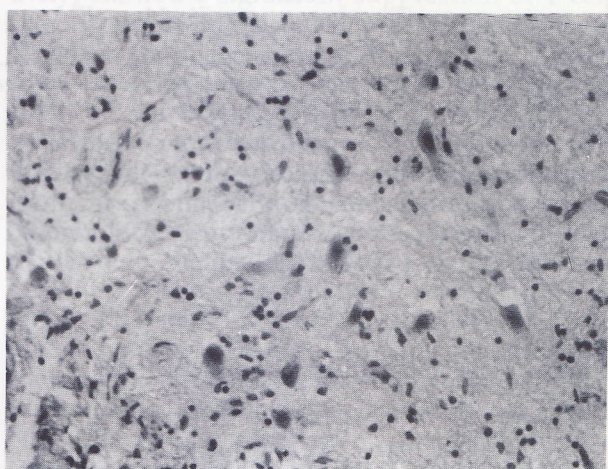


FIGURE 4 Fibrillary gliosis with large protoplasmic astrocytes in the demyelinated areas of (AOxDA)F<sub>1</sub> rat, 5 weeks after immunization

First remission - in contrast with the first attack, the relative number of perivascular cuffs was much lower. Predominant reactive astrogliosis and microgliosis were observed within the neural parenchyma (Figure 2).

Relapse the animals showed marked changes compared with the earlier stages of the disease. In the brain, mainly perivascular cuffs of mononuclear cells together with mild gliosis were found. Areas of demyelination were found predominantly in the lower thoracic and lumbosacral spinal cord but they could be seen in higher parts of the CNS, too (Figure 3).

Later stages of the disease - during the successive weeks reactive gliosis persisted but it was much less pronounced in comparison with the earlier stages.

Mononuclear cells invading the neural parenchyma were occasionally found (Figure 4).

#### Study of nonspecific systemic immunoreactivity

At regular intervals throughout the period of the experiment, the allogenic skin graft rejection time as well as the PFC counts were determined by longitudinal study in F<sub>1</sub> progeny of AOxDA strain (Table 2). The latent period was accompanied by a significant weakening of transplantation reactivity ( $p < 0.05$ ) when compared with the controls (untreated animals and animals treated with CFA alone) as we partially presented in our earlier reports<sup>13,15</sup>. During the further stages of the disease transplantation reactivity returned and persisted at a slightly subnormal level with complete normalization during the final remission. PFC counts were significantly elevated

TABLE 2 Immunoreactivity in different phases of recurrent EAE in hybrid (AOxDA)<sub>F1</sub> rats

	Phase of EAE	PFC/10 <sup>6</sup> splenocytes	No. of rats (P <sup>xx</sup> )	Y-59 skin graft rejection (days)	No. of rats (P <sup>xx</sup> )	Index of reactivity <sup>x</sup>	No. of rats (P <sup>xx</sup> )
Controls	Untreated animals	38±2.4	48	9.4±0.3	16	1±0.04	14
	Treated with CFA	21±5	12	8.9±0.5	9		
Experimental groups (CR-EAE)	Latent	267±53	12 (p<0.01)	12.3±0.2	6 (p<0.05)	1.8±0.14	8 (p<0.01) <sup>x</sup>
	Acute onset	322±68	12 (p<0.01)	10.2±1.2	6	1.7±0.15	8 (p<0.01) <sup>x</sup>
	First remission	402±99	12 (p<0.02)	10.1±0.3	6	2.1±0.20	8 (p<0.01)
	Relapse	153±18	12 (p<0.01)	9.6±0.2	6	1.8±0.09	8 (p<0.01)
	Second remission	346±104	12 (p<0.05)	10.3±0.2	6	1.8±0.10	8 (p<0.01)
	Chronic phase	76±14	12	9.5±0.7	6	1.3±0.19	8 (p<0.02)

<sup>x</sup>Index of reactivity = magnitude of skin reaction in relation to the size of vesicle post injection of encephalitogen  
<sup>xx</sup>P = the levels of significance in relation to controls

throughout the whole clinical course (Table 2). Fluctuations in transplantation and humoral reactivity after the latent period were not significant and did not correlate with the disease activity.

#### Study of specific cellular immunoreactivity

As shown in Table 2, the delayed type cutaneous reactivity in (AOxDA)<sub>F1</sub> rats was significantly elevated from the fifth day after the sensitization till the disappearance of clinical signs with peaks of reactivity immediately before the attacks of the disease.

## DISCUSSION

The present study has shown that juvenile (AOxDA)<sub>F1</sub> rats inoculated with xenogenic brain white matter developed clinical signs of chronic relapsing EAE in a high percentage of animals (80%). This result illustrates the age-related susceptibility to the clinical manifestation of CR-EAE that is similar to the observation in guinea pigs<sup>3</sup>. The mechanisms by which age influences the clinical course of the disease are possibly related to the integrity of the lymphatic organs (spleen, thymus)<sup>17</sup>. Moreover, there is increasing evidence of the crucial importance of the integrity of lymphatic organs in EAE induction and in the clinical course of the disease. Some authors reported about the existence of EAE effector cells or their precursors in thymus and spleen of naive Lewis

rats which can be induced by some procedures<sup>18,19</sup>. Additionally, it has been recently shown that there is an imbalance between the effector and suppressor elements depending on various organs in rats of Lewis strain suffering from CR-EAE<sup>14</sup>. In this regard it is interesting to note that chronic progressive and relapsing forms of EAE were rarely induced by sensitization only. In the above mentioned experiment, Ben-Nun et al. induced the disease by injecting guinea pig's basic protein in Freund's adjuvant<sup>17</sup>.

They obtained a chronic progressive form of the disease in splenectomized rats, and a relapsing form of EAE in thymectomized ones. In the latter group, the day of the disease onset was the day 11, with a recovery that followed after a few days, and a relapse at the day 20. Lublin succeeded in inducing a relapsing EAE in susceptible mice of SJL/J strain by a single inoculation of an emulsion containing allogenic spinal cord or MBP, Freund's adjuvant and pertussis vaccine<sup>20</sup>. It seems interesting to point out that the first clinical signs of the disease appeared relatively late after antigenic challenge (3 to 9 months) and were followed by a relapsing-remitting course of the disease.

It is rather surprising that the chronic relapsing form of EAE in our experiment was produced without interruption of the integrity of the immune system, which was necessary in the experiments on rats described (i.e. splenectomy, thymectomy).

The experiments using (susceptible x resistant) strain F<sub>1</sub> and back-cross progeny have shown that EAE susceptibility and resistance are tightly linked to the immune response-EAE (Ir-EAE) locus of MHC,

but could be influenced by non-MHC genes as well<sup>5,6,7</sup>. The fact that CR-EAE in our experiment was induced in a high percentage in hybrids F<sub>1</sub> of a highly susceptible DA strain and low susceptible AO strain (and in a low percentage in DA strain) is pointing to the genetic influences in the broader sense of the word. In this regard, the susceptible DA rats possess AgB<sup>4</sup> haplotype, while AO rats possess AgB<sup>2</sup> allele. All the animals of F<sub>1</sub> progeny showed the EAE susceptibility comparable to that of the DA rats. The fact that in our experiment susceptibility was not influenced by sex, supports the thesis of a dominant autosomal inheritance of EAE susceptibility and probably of CR-EAE susceptibility.

The finding that only 10% of AO rats showed mild signs of EAE in our experiment is in line with earlier observation made by Mostarica-Stojković et al<sup>21</sup>. Moreover, they showed that AO rats do possess lymphocytes sensitive to the antigenic determinant of rat MBP and that the resistance to EAE induction could be partially overcome by the low dose of irradiation or by pre-treatment with cyclophosphamide. A similar finding was observed in PGV strain<sup>22</sup>. These experiments showed that the strains AO and PGV already carried Ir-EAE genes but that the immunological disease was somehow suppressed. The overcoming of the suppression could be explained by either the changes in the genetic regulation of the suppressor mechanism<sup>23</sup> or by a disbalance between suppressor T-cell lines and effector cells recently demonstrated<sup>24</sup>.

Our recent experiments also support this view. We found that splenectomy and a low dose of cyclophosphamide abolished the complete resistance to the reinduction of EAE in DA rats and subsequently all the rats developed classical clinical signs of a severe form of the disease. The effect of such treatment on the reactivity in hybrids (AOxDA)F<sub>1</sub> was similar but much less pronounced (to be published). In other words, it could be supposed that the susceptibility to EAE induction is also dependent on the quantitative difference in the suppressor cell activity.

Pathologic changes during the first attack in our model of CR-EAE consisted of perivenous infiltration of mononuclear and polymorphonuclear cells, macrophages and rarely eosinophils. The lesions involved both white and gray matter of neural parenchyma. However, in the next stage a relatively small number of the earlier lesion accompanied by a high degree of reactive gliosis were found. Lesions of different morphology were found during the relapse phase. At this stage, the most remarkable findings were areas of demyelination in the spinal cord (predominantly in the lower region) and brain (predominantly in the cerebellum). During the later stages of the disease inflammation was a minor feature, while reactive gliosis was invariably present. This picture is very similar to the patterns seen in

CR-EAE of strain 13 and Hartley guinea pigs<sup>4</sup>. In general, a good clinico-pathological correlation was observed during the first and the second attacks, i.e. active clinical disease, while the lesions found during the first remission and the later stages of the disease, i.e. inactive clinical disease, obviously did not produce any clinical symptoms.

A number of abnormalities of cellular and humoral immune response to various EAE inciting antigens have been reported (for review see: Paterson, 1977)<sup>25</sup>. The present study showed a temporal kinetic pattern of nonspecific humoral, and nonspecific as well as specific cellular reactivity during the clinical course of CR-EAE. Our results of the humoral immune studies have shown a consistent elevation of PFC associated with nonsignificant fluctuations between the initial attack and the second remission phases. The results of the nonspecific cellular immune response investigation (transplantation reactivity) showed a significant suppression of T cell activity only during the latent period, followed by a slightly subnormal reactivity throughout the successive stages<sup>15</sup>. On the other hand, the delayed type of cutaneous reactivity to CNS-antigen was significantly elevated from the fifth day post-immunization till the complete remission of the clinical disease with the peaks of reaction just before the disease attacks<sup>26,27</sup>. These findings support our earlier hypothesis about competition between the specific and nonspecific immune reaction outside the CNS during the latent interval of the disease, which is probably necessary for the development and localization of abnormal lymphocytes in the CNS. The clinico-pathological changes observed in our model of CR-EAE point to a local immunoregulatory disorder within the CNS as the main operative mechanism that underlies the disease activity after the latent period, but which is relatively independent of the immune system outside the CNS. The observed immune dysregulation established from the very early phase of the disease throughout the whole clinical course is probably related to genetic factors which regulate the various repertoire of T cell activity to encephalitogenic determinants<sup>28,7</sup>. Since a similar observation has been made in exploring the T cell repertoire in patients with MS<sup>29</sup>, this adds yet another aspect of suitability of CR-EAE model for MS investigation.

Further studies to analyze the complex interrelationship between the CNS immunoreactivity and the genetic regulatory mechanisms are in progress in our laboratory.

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## KRONIČNI RELAPSIRAJUĆI EKSPERIMENTALNI ALERGIJSKI ENCEFALOMIJELITIS U ŠTAKORA: KLINIČKOPATOLOŠKI TIJEK, GENETIČKI I IMUNOLOŠKI ASPEKTI

### IZVORNI ZNANSTVENI ČLANAK

*Ključne riječi:*

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**SAŽETAK** Eksperimentalni alergijski encefalomijelitis induciran je u štakore različitih genotipa aktivnom imunizacijom encefalitogeničnim ekstraktom telećeg mozga. Kronična relapsirajuća klinička bolest primijećena je u juvenilnog F<sub>1</sub> potomstva Albino Oxford mužjaka i Dark August ženki u velikom postotku koji je varirao od 65% do 75% od niza do niza eksperimenata, a u Dark August vrsti iznosio je samo od 20% do 25%. U ovom radu prikazujemo sintezu kliničkopatoloških, genetskih i imunoloških aspekata bolesti u štakora. Naši rezultati potvrđuju (1) veliku sličnost u morfologiji lezija centralnog živčanog sustava kronične relapsirajuće kliničke bolesti i multiple skleroze, (2) važnost stanične imunosti u patogenezi eksperimentalnog alergijskog encefalomijelitisa, (3) činjenicu da je osjetljivost na eksperimentalni alergijski encefalomijelitis uvjetovana genetski i (4) postojanje sistemske imunodne regulacije u kroničnoj relapsirajućoj kliničkoj bolesti.

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### INTRODUCTION

Experimental allergic encephalomyelitis (EAE) is a T-lymphocyte mediated autoimmune disease of the central nervous system (CNS) which can be induced in susceptible animals by immunization with

CNS extracts or a myelin basic protein (MBP) administered in an appropriate adjuvant. In the case of chronic relapsing form of the disease (CR-EAE), EAE serves as the best experimental animal model for the pathogenic study of multiple sclerosis (MS). From the clinical-pathological point of view there are close similarities between the animal and the human