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Pathogenesis of Borna disease

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Summary. Borna disease represents a unique model of a virus-induced immunological disease of the brain. Naturally occurring in horses and sheep, the mechanisms of pathogenesis have been studied in experimental animals, namely in the rat. Many investigations have revealed that the infection of the natural hosts principally follows the same pathogenic pathways as observed in rats, leading to a severe encephalomyelitis. This affliction of the central nervous system results in severe neurological disorders that again, are fully comparable in laboratory animals to those in the natural and the different experimental hosts. In addition, alterations have been reported which are also based on the infection of the brain and do not result in the classical encephalitic clinical picture but rather in alterations of behavior. However, to all of our knowledge, the various clinical pictures of Borna disease are not caused by the infecting virus itself but rather by the hosts immune response towards it, i.e. by a virus-induced cell-mediated immunopathological reaction. The importance of virus-specific CD4+ T cells as exemplified by a cultured T cell line and of CD8+ T cells as shown by immunomodulatory substances and specific antibody treatment in vivo for the pathogenesis of acute Borna disease will be elucidated here. In addition, evidence will be provided that virus-specific CD8+ T cells are also responsible for the dramatic brain atrophy in the chronic phase of the disease in rats. Therefore, Borna disease not only lends itself exquisitely well to the study of the pathogenesis of an immunopathological disease of the brain but also represents one of the few models for immune-mediated tissue destruction that eventually leads to brain atrophy and clinically to dementia.

Introduction

Afflictions of the central nervous system have not only been in the focus of scientific research since most recently, when pathological alteration

caused by viruses or virus-like agents have attained public interest. Most prominently, the presence of HIV-1 antigen in the brains of human patients suffering from dementia [26] and the most recent appearance of "mad-cow disease" caused by the yet unidentified "Scrapie agent" might be mentioned. Many autoimmune and virus-induced immunopathological alterations of the brain have been studied in experimental animals and serve as models for animal and human diseases. In the classical example, infection of mice with the lymphocytic choriomeningitis virus and recently also in Theiler virus infection in mice, the presence and the pathogenic importance of a virus-specific immune response, especially mediated by T cells, has been demonstrated in the brain [6, 10]. Other models studied in rodents include corona virus and measles virus infections in rats where an autoimmune reaction is of crucial importance in the pathogenesis of virus-induced diseases of the brain [19]. In addition to HIV in AIDS encephalopathy, several observations in human patients support this view, namely the detection of measles virus in cases of subacute sclerosing panencephalopathy [33], and of papovavirus in progressive multifocal leukoencephalopathy [22, 41]. Furthermore, several viruses have been suggested to be involved in the development of multiple sclerosis [18].

In general, the outcome of a viral infection depends on characteristics of the virus and the efficiency and speed of the immune system including natural defense mechanisms to react to the invading agent. Viruses that cause cytopathogenicity are a much greater threat to the host than viruses that are non-cytopathic. Consequently, the evolution of the immune system has been significantly influenced by the demand for an efficient and rapid elimination of cytolytic viruses to avoid widespread infection and reduce tissue destruction. However, this strategy of a highly efficient immune reaction bears a considerable disadvantage for the host in the case of infection with persistent viruses lacking cytopathogenicity, since the immune system is apparently not capable of distinguishing between cytolytic and non-cytolytic viruses. The result may be damage to the host by an immune reaction although the agent that induced the immune response is otherwise perfectly innocuous.

Borna disease and Borna disease virus

An example of such a non-cytolytic virus is Borna disease virus. The virus and, respectively, the disease has been named after the town of Borna in Saxony, where in 1895 an endemic among horses of a cavalry regiment resulted in the loss of a high number of animals. By that time, the disease had already been recognized for about 100 years but

was known under various synonyms reflecting central nervous system disorders. A particular characteristic of the disease is the variably long incubation period that was the reason why BD has been grouped with "slow" virus infections. The disease is associated with disturbances of motility and in sensory functions and usually results in paralysis and death in affected natural hosts [reviewed in 16]. Pathohistologically, BD is classified as a progressive polioencephalomyelitis with pronounced inflammatory reactions in the basal cortex, the nucleus caudatus and the entire hippocampal area.

BD virus has been only recently characterized as an RNA virus [7, 15, 17, 30, 39] with strong evidence for negative-sense polarity [3, 7]. The virus which is tightly cell associated and apparently lacks cytopathogenicity in vitro and in vivo replicates preferentially in cells derived from the neural crest [12]. However, after cocultivation [12] or after repeated infection with virus-containing supernatants from the brain of infected rats, other cell types such as cultured astrocytes [27, 28] and skin cells [25] also can be directly infected in vitro.

After experimental infection, a wide variety of animals can be infected including species phylogenetically distant, such as birds and non-human primates. Recently, BDV-specific antibodies have also been detected in humans, indicating a possible role of BDV as a human pathogen [reviewed in 31].

The species that has been studied most intensively is the rat and most if not all progress in understanding the pathogenesis of this virus-induced disease of the central nervous systems was achieved by using this experimental animal.

After i.c. or i.n. infection of adult rats infectious virus and virus-specific antigen can be detected in high concentrations (Table 1) in the

Table 1. Consequence of BDV infection in adult rats

Disease	Acute ← → Chronic			
Symptoms	hyperactivity, aggressiveness ataxia, pareses (paralyses)		ataxia, somnolence, chron. debility, dementia	
Pathology	↓ +++ inflammation ——— ++ — + — ± — ⁻ —			
	→ brain cell degeneration ——→ cortical brain atrophy ——→			
Virus (brain)	± positive ———			
(retina)	± positive ——— negative ———			
	↑ BDV	⊥ 2 wk	⊥ 4 wk	⊥ 8 wk	⇔ natural lifespan

brain, the retina, the cerebrospinal fluid, in peripheral nerves and in the adrenal gland [1, 4, 5, 8, 20, 21, 36]. At later stages of the infection the virus disappears from the retina, but a persistent productive infection is maintained in the other tissues mentioned above. In parallel to the loss of virus from the eye, the animals go blind. In immunocompetent infected rats, disease symptoms such as lack of grooming, ataxia, hyperactivity and aggressiveness can be seen at about day 14 (Table 1). This acute phase of the disease lasts for about 3 weeks and later results in apathy, somnolence, progressive ataxia and paresis and sometimes results in paralysis and death. The clinical symptoms are paralleled by the development of an inflammatory reaction in the brain that is localized mainly perivascularly (Fig. 1). However, encephalitic lesions are also found in the brain parenchyma. In general, the inflammation is initially centered in the limbic system but spreads to other areas of the brain during infection [8, 20]. The chronic phase of BD is clinically governed by increasing apathy and the rats remain in a severe somnolence, show signs of dementia and behavioral abnormalities [9, 21]. Some rats, however, develop an impressive obesity with body weights of up to 500–600 g without clinical disease as compared to 200 g of uninfected adult rats. The histopathological picture of the chronic disease, which can be diagnosed after day 60, is characterized by a significant decrease of the inflammatory reaction and the development of a severe hydrocephalus internus.

Immunopathogenesis of Borna disease

Significantly different pictures are seen in rats that show natural or drug-induced immunoincompetence. Newborn, athymic, cyclophosphamide or cyclosporine A treated rats do not show Borna disease or the acute inflammatory reaction (Table 2). However, virus-specific nucleic acid and infectious virus, in addition to virus-specific antigen, is found in these animals in amounts comparable to fully immunocompetent rats [4, 13, 20, 25, 36, 37]. Most strikingly, immunocompromised rats show no destruction of the retina, although the virus persists in the eye, i.e. the rats do not become blind despite the presence of virus in retinal layers (Table 2) [20]. This fact shows perfectly well that BDV has very low or even no direct cytopathogenicity in vivo. The importance of the immune response for the pathogenesis was further stressed by showing that adoptive transfer of lymphocytes from BDV-immune rats into immunoincompetent animals resulted in full-blown BD [20, 37]. As a whole, these facts together demonstrate that BD is based on a virus-induced immunopathological reaction rather than on a direct virus-cell inter-

Table 2. Consequence of BDV infection in newborn, athymic or immunosuppressed rats

Disease			No symptoms		
Pathology			No inflammation		
Virus (brain)	±	positive →			
(retina)		±	positive →		
				⇔	
	↑	⊥	⊥	⊥	
	BDV	2 wk	4 wk	8 wk	natural lifespan

Table 3. Inhibition of BD after long treatment with CSA

Wk after CSA treatment		Duration of CSA treatment			
		–	2	3	4
5	disease	+	+	+	–
	encephalitic lesions	+++	+++	+/++	–
	antibodies	2,560	<40	<40	<40
20	disease	+	+	+	–
	encephalitic lesions	+	+	+	–
	antibodies	5,120	5,120	<40	<40
60	disease	+			–
	encephalitic lesions	+/–	ND	ND	–
	antibodies	5120			<40

Rats were treated with CSA doses of 25 mg/kg/day given s.c. starting one day before infection for various time intervals; antibody titers are expressed as the reciprocal of end-point dilution

action. The possibility that antiviral antibodies play a significant role in the pathogenesis of BD can be excluded according to a variety of experimental evidence [13, 20]. The most decisive argument against the involvement of antibodies in the pathogenesis of BD comes from experiments with the immunosuppressive drug cyclosporine A. Rats treated with CSA at appropriate doses and for a sufficiently long time can be protected from BD and do not mount an antibody response (Table 3) [37]. However, suboptimal treatment of BDV infected rats with CSA results in the development of an encephalitis in the absence of an anti-BDV antibody response (Table 3). Although these findings clearly indicated that the pathogenesis of BD is closely related to the cellular immune response, they did not reveal the cellular basis of the immunopathological process resulting in inflammation of the brain. By characterizing the cells present in the inflammatory lesions, employing

Table 4. Adoptive transfer of a BDV-specific CD4+ T cell line into BDV-infected immunosuppressed rats

BDV infection	Immunosuppression	T cell transfer	Disease[a]	Encephalitis[a]
+	−	−	3/3	3/3
+	+	−	0/3	0/3
+	+	+	8/8	8/8
−	+	+	0/3	0/3

BDV-specific T cells were passively transferred i.v. immediately after in vitro restimulation at concentrations of 1×10^6 to 8×10^6. Recipients were immunosuppressed 1 day after i.c. infection by intraperitoneal injection of a single dose of 150 mg/kg cyclophosphamide.

[a] Number of rats per experimental group

immunohistochemical methods, a useful approach was found to solve this question. Immunohistological investigations into the quality of cells involved in the perivascular inflammatory reaction revealed the presence of CD4+ and CD8+ T cells in addition to numerous macrophages and B cells (Fig. 1) [8]. To elucidate the importance of T cell subsets in the pathogenesis of BD in a first approach, a homogeneous virus-specific T cell line was established. Lymphocytes obtained from regional lymph nodes after subcutaneous immunization with purified virus-specific antigen were cultured and restimulated in vitro employing a protocol for the cultivation of CD4+ T cells [29]. Analysis of this cell line revealed BDV-specificity, MHC class II restriction and the phenotypical markers of CD4+ helper/inflammatory cells. Adoptive transfer of this cell line into BDV-infected immunosuppressed healthy recipients resulted in severe disease and death as early as day 5 after the injection of effector cells (Table 4) [28, 29]. In contrast, passive transfer into uninfected rats did not result in encephalitis or disease, which shows that this BDV-specific T cell line by itself is not encephalitogenic. These results, together with the immunohistological characterization of inflammatory cells in the brain of BDV-infected rats, strongly suggest that BD is caused by a delayed type hypersensitivity reaction (DTH). The finding of the importance of MHC class II restricted T cells agrees with the presence of MHC class II antigen in the brain of BDV-infected rats. This self antigen is detected on various cell types upon immunohistological characterization, namely perivascularly but also on oligodendrocytes, microglial and ependymal cells (Fig. 2) [8, 29, 35].

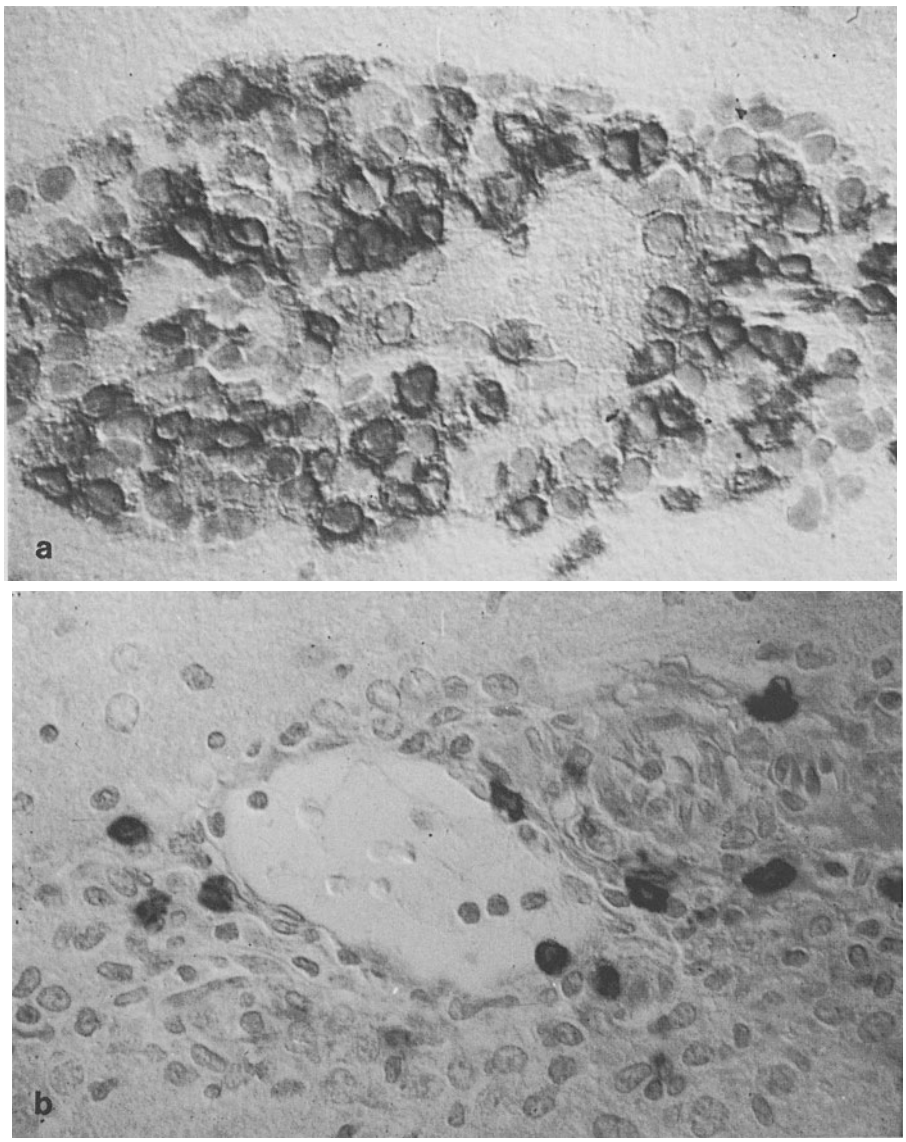

Fig. 1. Immunhistological characterization of cells in perivascular infiltrates of BDV-infected rats. Frozen sections from brains were reacted in a peroxidase anti-peroxidase reaction with a monoclonal antibody specific for CD4+ T cells (**a**) or specific for CD8+ T cells (**b**)

The importance of these cells in the pathogenic mechanism has not yet been determined, especially since it has not yet been possible to demonstrate their role in antigen presentation of BDV-specific antigen in the brain. However, some evidence has accumulated that provides better insight into the mechanisms of pathogenicity and the T cell subsets involved. With regard to MHC class II it was shown that the elevation of the expression of this self antigen by IFN-γ increased the proliferative

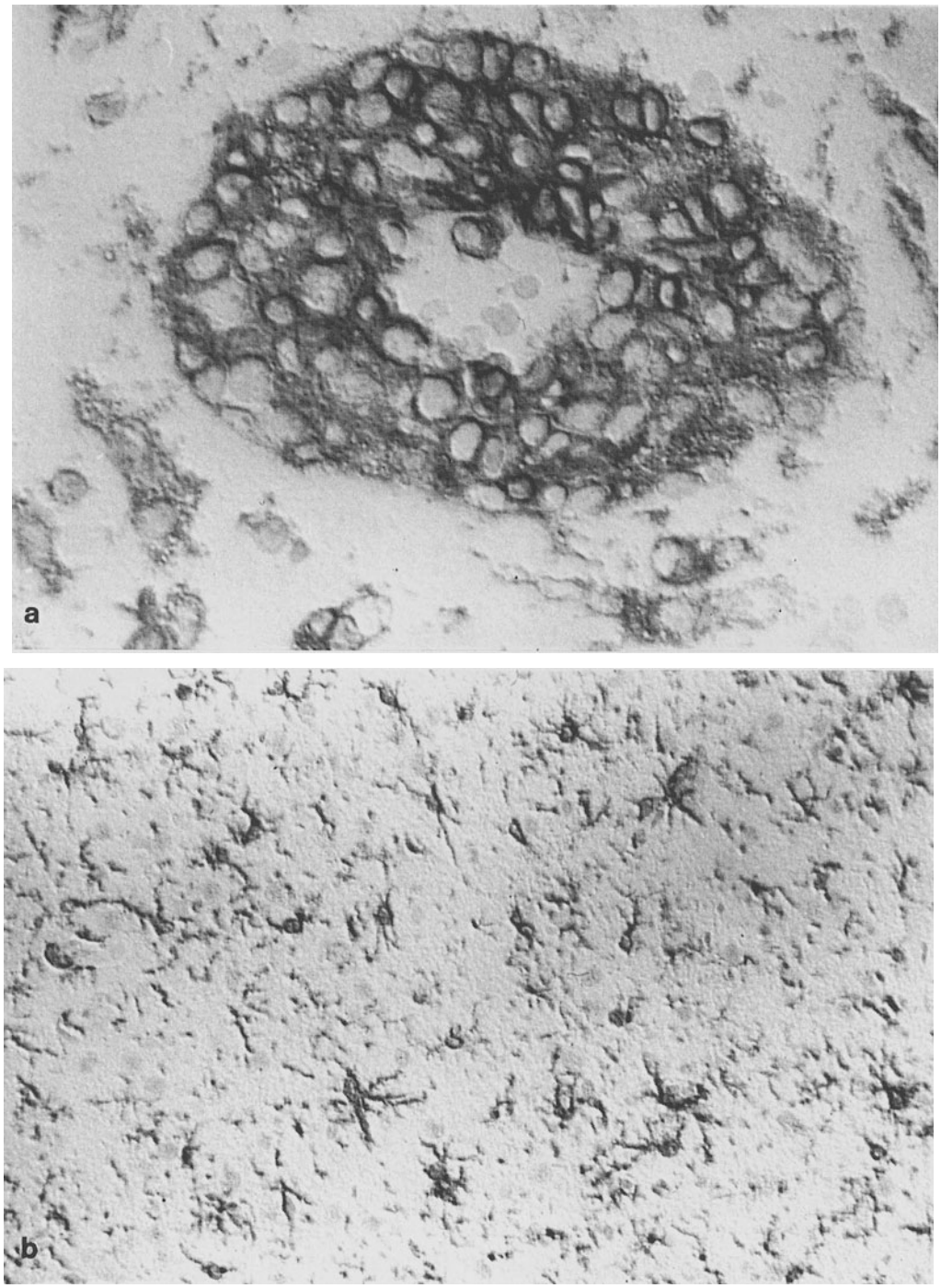

Fig. 2. Demonstration of MHC class II antigen expression in the brain of BDV-infected rats. Massive perivascular class II expression (**a**) and MHC class II-positive cells in the parenchyma, presumably activated microglia (**b**). Sections were incubated with an MHC class II-specific monoclonal antibody

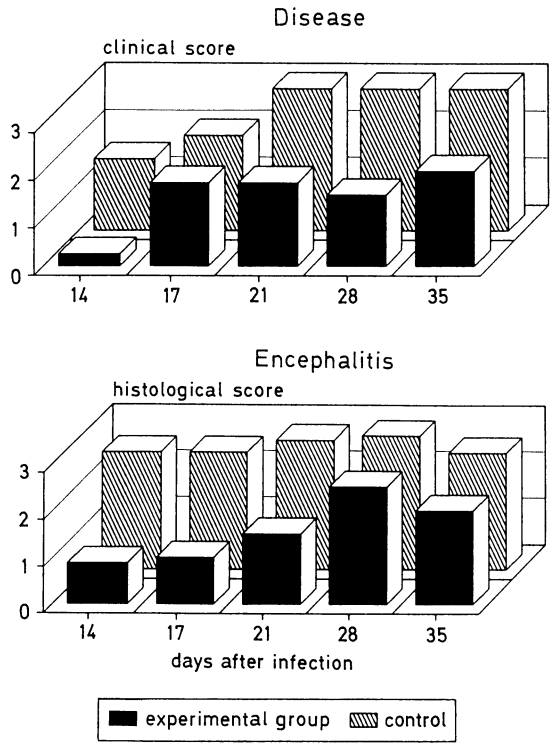

Fig. 3. Mean clinical and histological scores of BDV-infected rats treated with recombinant human transforming growth factor-β2 (TGF-β2; 1 μg/day i.p. 1 day before infection through day 7 after infection) and infected rats without further treatment

capacity of the BDV-specific CD4+ T cell line in vitro [29]. Likewise, the expression of MHC class II on BDV-infected astrocytes used as target cells proved to be a prerequisite for in vitro cytotoxicity by the same cell line [27].

These in vitro findings suggest that lymphokines and, obviously especially IFN-γ and, the cells capable of producing this type of interferon might be of crucial importance in the pathogenesis of BD [32]. This assumption could be substantiated in experiments employing the transforming growth factor β2 (TGF) in vivo [35]. TGF belongs to a class of polypeptides exhibiting diverse effects on cell growth and differentiation. These substances act as multifunctional cytokines with potent inhibitory activity on growth, differentiation and effector functions of activated T and B lymphocytes as well as macrophages [reviewed in 23, 40]. Experiments with TGF-β2 in BDV-infected rats revealed a reduction of the severity of clinical symptoms that was paralleled by a significant reduction of the inflammatory reaction in the brain (Fig. 3). However, the efficacy of the treatment was only transient. Immunhistological investigations revealed slightly reduced CD4+ T cell numbers

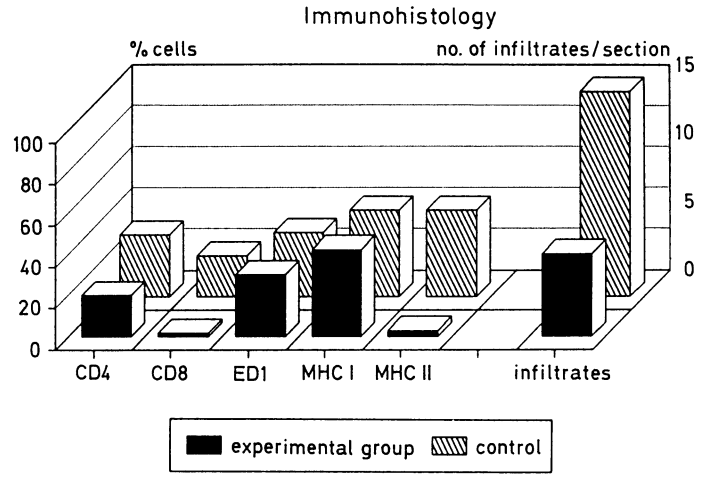

Fig. 4. Histological and immunohistological evaluation of encephalitic lesions in TGF-β2 treated and untreated BDV-infected rats. The columns on the right represent the mean number of infiltrates/section, the columns on the left show the percentage of positively immunostained cells in the infiltrates

and no changes in macrophage counts in encephalitic lesions of TGF treated rats. However, this study provided first evidence for the pathogenic importance of CD8+ T cells in BD (Fig. 4). Whereas other cell populations present in perivascular inflammatory lesions were not significantly altered, as mentioned above, CD8+ T cells were virtually absent from encephalitic lesions. Furthermore, the expression of MHC class II antigen was significantly reduced in the brain of TGF-treated Borna disease virus-infected rats, whereas MHC class I expression was not. We had shown previously that neither in the brain of infected rats [35] nor in astrocytic cultures in vitro [25, 27, 29] the virus by itself induced the expression of MHC class II, but IFN-γ was able to do so. Since CD8+ T cells are potent producers of immune interferon and IFN-γ on its turn regulates MHC class I and class II expression, the absence of CD8+ T cells in the brain of TGF-treated rats might result in the observed reduction of MHC class II antigen [34]. Our recent finding that BDV-infected astrocytes produce in vitro IFN of the α/β type that shows all characteristics of a previously described astrocyte-IFN [38] agrees with this interpretation [25]. α/β IFN and, in particular, IFN produced by astrocytes upregulates MHC class I but not class II expression [11, 38] which would explain the IFN-γ independent presence of MHC class I in TGF-treated rats. The experiments performed with TGF-β revealed an initial drastic reduction of the local immune response after BDV-infection. The relative absence of CD8+ T cells seemed to be decisive, since the production of soluble mediators that induce the expression

of MHC antigen is hampered. Interestingly, and fully supporting this hypothesis, the increase of CD8+ T cells late after TGF treatment was directly correlated with an increase in the expression of MHC class II antigen in the brain and encephalitic lesions (Fig. 4). In all, the reduced expression of restriction elements for cell-mediated immune response leads to an initial inhibition of the encephalitic reaction and clinical symptoms due to a relative absence of restriction elements despite the presence of CD4+ T cells.

Additional evidence for the pathogenic importance of CD8+ T cells in BD comes from experiments in which BDV-infected rats were treated with monoclonal antibodies directed against various T cell markers [36]. Antibodies specific for CD4+ and CD8+ cells were able to decrease or even prevent the local inflammatory reaction if given early during the infection. However, CD8-specific monoclonal antibodies appeared to be much more effective and easily prevented the immunopathological disease whereas antibodies directed against CD4+ cells were significantly less effective (Table 5). These findings fully agree with the above mentioned result that CD8+ T cells play an important role in the pathogenesis of BD insofar as cells of this phenotype have been shown to be potent producers of cytokines. We therefore proposed a sequential role of an initial CD8+ T cell response that is decisive in triggering the local CD4+ T cell-mediated delayed type hypersensitivity reaction in the brain after BDV infection [34, 36].

From experiments employing monoclonal antibodies directed against CD8+ cells, an explanation for another characteristic feature of Borna disease, namely brain atrophy became obvious. As mentioned before, the chronic phase of BD is characterized by a prominent cortical atrophy (Fig. 5a) and chronic debility [20]. In a recent study we could demonstrate that, in addition to the inhibition of the immunopathological reaction, treatment of BDV-infected rats with anti-CD8 monoclonal antibodies resulted only in minimal brain-cell lesions and no obvious loss of brain substance could be seen even long after infection (Fig. 5b) [2]. In untreated rats necrobiotic changes of brain cells were found to be present from early stages of the disease and neuronal cell loss was one of the most prominent features of BD. By characterizing the brain cells that express MHC class I antigen it became evident that this self antigen could be demonstrated on neurons and astrocytes [2, 25]. The most intriguing finding upon histology was the coincidence of the occurrence of CD8+ cells and a dramatic increase of MHC class I on the one hand, and the presence of first neuronal degenerations on the other. In rats depleted of CD8+ T cells in vivo, no marked amounts of MHC class I antigen was detected in the brain parenchyma, whereas MHC class II expression was not different in any of the BDV-infected rats, regardless

Table 5. Effect of in vivo administration of monoclonal antibodies directed against CD4+ or CD8+ T cells on encephalitis and disease after BDV infection

Monoclonal antibody	Specificity	Administration on days	Weeks after infection					
			3		4		8	
			lesions	disease	lesions	disease	lesions	disease
OX-52	CD4, CD8	−1, +1	0.2	0	0	0	0	0
W3/25	CD4	−1, +1	3.0	2.0	1.5	3.0	1.5	2.0
		−1, +1, +7, +14	1.0	0.5	2.0	2.0	1.5	1.0
OX-38	CD4	−1, +1	3.0	2.25	2.5	2.75	n.d.	n.d.
		−1, +1, +7, +14	0	0	0.5	0.25	0	0
OX-8	CD8	−1, +1	0.5	0	0.5	0	0.25	0.25
control	untreated	–	2.75	2.5	2.75	2.5	2.0	2.75

Brain tissue sections were scored on an arbitraty scale ranging from 0 to 3.0 based on the numbers of infiltrates per section and the number of cell layers present in each infiltrate. The disease symptoms were scored on an arbitraty scale from 0 to 3.0 based on the general state of health and the appearance of neurological symptoms. n.d. Not determined

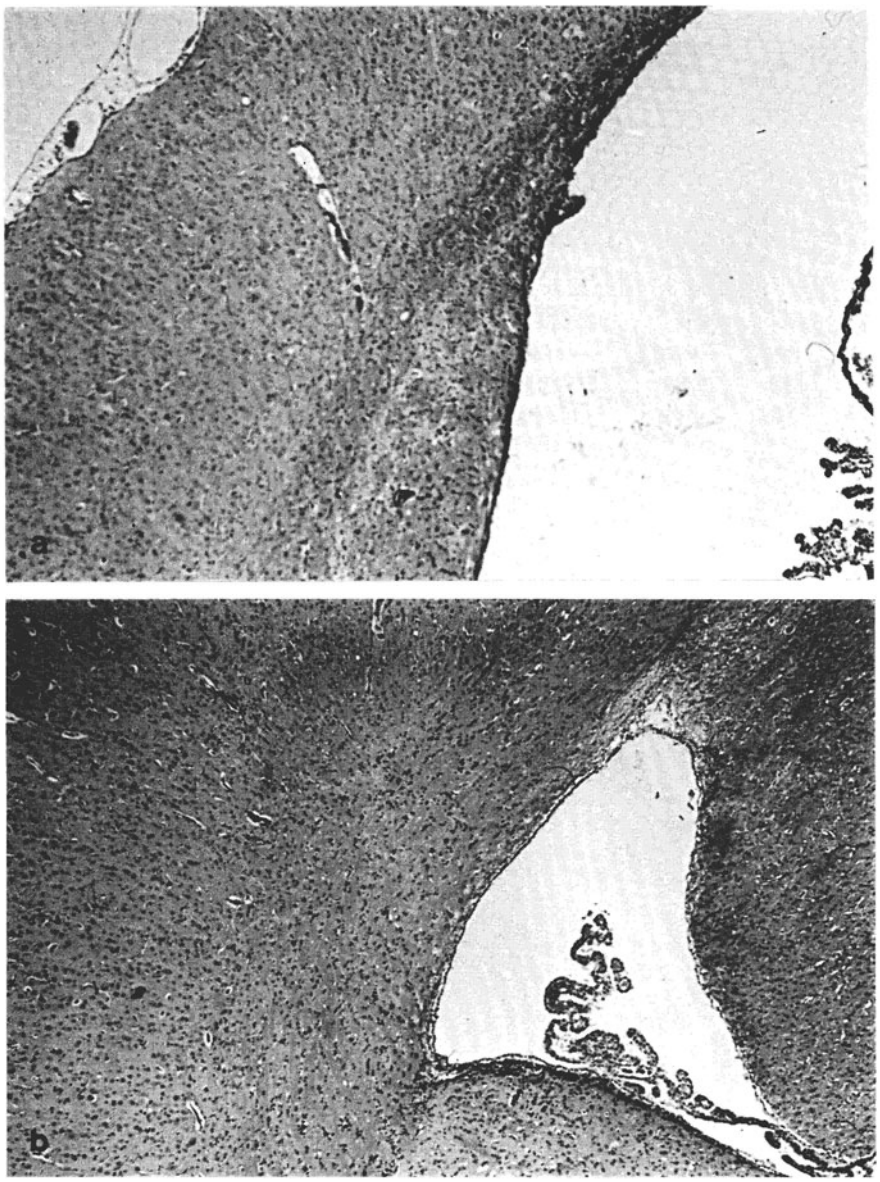

Fig. 5. Severe cortical brain atrophy in an adult untreated rat 8 weeks after BDV infection. Note the "burned-out" inflammation and the enormously dilatated ventricle (**a**). Brain section of a BDV-infected rat treated with a monoclonal directed against CD8+ T cells. Note the complete lack of atrophy or signs of inflammation (**b**)

of whether treated with anti-T cell antibodies or not. Since coexpression of MHC class I antigen in association with virus-specific proteins renders cells as targets for cytotoxic CD8+ T lymphocytes [reviewed in 42], we consequently looked for cytotoxic T cell activity in BDV-infected rats. Employing syngeneic and allogeneic BDV-infected target cells we could demonstrate virus-specific cytotoxic T cell activity (Table 6) [25].

Table 6. Cytotoxic activity in lymphocyte preparation isolated from the brain of BDV-infected rats

Type of target cell	% Lysis of target cell
Syngeneic BDV-infected	45
Syngeneic uninfected	3
Allogeneic BDV-infected	5
Syngeneic BDV-infected	40
Syngeneic uninfected	5
Syngeneic BDV-infected in the presence of Anti-MHC class I antibody	7

Lymphocytes from the brain were isolated on a modified RPMI/Ficoll gradient [25]. Specific lysis was determined after a 9 h coincubation of effector cells with ^{51}Cr labeled target cells. Effector: target ratio 30:1

Blocking experiments using antibodies directed against MHC class I antigen provided further evidence for the presence and activity of classical cytotoxic T lymphocytes in the brain of BDV-infected rats (Table 6).

Conclusion

In this short review we have summarized the present knowledge of the pathogenesis of Borna disease and presented data that help describe the cellular basis of this immunopathological disease of the brain. From all of our work it becomes apparent that interactions and the interplay among the components of the cellular immune response and between the cellular immune system and lymphokines are of crucial importance. As exemplified by immunosuppression and immunomodulation with various drugs, understanding of the pathogenetic pathways is the inevitable prerequisite to possible interference with disease processes. Here, we also show that Borna disease is not only a useful model of a virus-induced immunological disease but we have also provided evidence that the experimental disease in rats presently possibly represents the best model for studying *in vivo* cytotoxicity exerted by classical CD8+ cytotoxic T lymphocytes.

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