Invasion of the Brain and Chronic Central Nervous System Infection after Systemic *Mycobacterium avium* Complex Infection in Mice

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Central nervous system (CNS) infections caused by nontuberculous mycobacteria have been described previously, especially in patients with AIDS. To investigate specific aspects of the pathogenesis of this entity, C57BL bg^+/bg^- mice were infected intravenously with *Mycobacterium avium*, and cultures of blood and brain as well as histopathology examination of brain tissue were carried out at several time points up to 6 months after infection. Low-grade inflammatory changes with small aggregates of lymphocytes and macrophages as well as perivascular cuffing were seen early in the infection. A small number of bacteria could be observed in the parenchyma of the choroid plexus. Six months after infection, numerous bacteria were present within the foamy macrophage of the granulomatous lesions along the ventricle and meninges. None of the mice developed clinical signs of meningitis or encephalitis or even died spontaneously during the period of observation. Use of CD18$^{-/-}$ knockout mice indicated that transport of the bacterium within neutrophils or monocytes into the brain is unlikely. Mild chronic CNS infection developed in the mice during sustained systemic *M. avium* infection, similar to what has been reported in most human cases.

Central nervous system (CNS) infections due to nontuberculous mycobacteria (NTBM) usually manifest as meningitis or meningoencephalitis, but occasionally pure encephalitis or abscesses along neuraxes are found (5, 9). NTBM brain diseases are most often described in patients with AIDS or other immune-compromised patients, but it had also been reported in individuals without obvious underlying disease (5, 26, 28). CNS infections with NTBM can sometimes be misdiagnosed as *Mycobacterium tuberculosis* infection, resulting in incorrect treatment and death (11, 28). As the epidemic of human immunodeficiency virus infection and the application of immunosuppressive treatment expand, it has become more likely that doctors might come in contact with these usually infrequent infections. A suitable animal model may therefore help us to understand the immunopathophysiology of this disease, as well as to develop an effective therapy.

The *Mycobacterium avium* complex is the most common organism causing systemic opportunistic bacterial infections in patients with AIDS (13, 14, 29). It is also the leading cause of the NTBM brain disease in this population (5). Patients with *M. avium* infection usually have disseminated disease with bacteremia and frequently liver, spleen, bone marrow, and lymph node involvement. In addition, a variable percentage of these patients can have invasive infection in the brain (6, 11, 12, 15, 17, 27).

Murine models of disseminated *M. avium* infection have been developed since 1983 (2, 3, 10) and used extensively in the investigation of host response and in the screening of active therapeutic agents (1). In these models, bacterial burden and histopathology changes in the abdominal organs and lymph nodes had been thoroughly studied, but the neuraxes have not been evaluated.

The CNS is confined to an anatomic closed space, separated physically and immunologically from the rest of the body by the rigid bony cage of the skull as well as the blood barrier. Therefore, the clinical presentation, immune response, and drug treatment may be quite different for CNS infection and peripheral systemic infection with the same pathogen.

In an attempt to improve our knowledge about the pathogenesis of CNS infections caused by *M. avium*, we developed a murine model that shows brain pathology following bacteremia.

Four-month-old female C57BL bg^+/bg^- mice and C57BL/6J-Itgb2 (CD18$^{-/-}$ knockout [KO] mice) weighing 20 g (Jackson Laboratory, Bar Harbor, Maine) were used for the experiments. Mice were briefly anesthetized by halothane inhalation before inoculation of bacteria. *M. avium* strain 101 (serovar 1) was isolated from the blood of a patient with AIDS (3). *M. avium* organisms were cultured for 10 days at 37°C on Middlebrook agar 7H11 medium (Difco Laboratories, Detroit, Mich.) supplemented with oleic acid, albumin, dextrose, and catalase (OADC; Difco). Transparent colonies were suspended in Hanks' buffered salt solution (HBSS) and adjusted to the desired concentration by comparison with a McFarland turbidity standard. Samples obtained from the bacterial suspension were plated onto Middlebrook 7H11 agar to confirm the inoculum size. One hundred microliters of bacterial suspension was used for intravenous (i.v.) injection, and 40 µl of bacterial suspension was used for intracerebral (i.c.) injection.

In a preliminary protocol, we attempted to define the minimal doses required to obtain brain infection when bacteria were administered by i.c. inoculation. Mice were transiently anesthetized by halothane inhalation and challenged i.c. with 1.2×10^3, 1.2×10^4, or 1.2×10^6 organisms of *M. avium*. According to the method described by others (18), 40 µl of bacterial suspension was delivered through a 27-gauge needle by direct puncture into the cranium at the midline, 4 mm posterior to the orbit. At 1, 4, 8, and 78 days, the brain was obtained and homogenized, and the bacteria were quantitated after plating. In an alternative protocol that resembles the human infection, we infected mice with *M. avium* i.v. Three

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TABLE 1. Bacterial load in blood and brain after infection by different routes

Time postinfection	Sample	Mean no. of bacteria[a] (log CFU) ($n = 3$)			
		10^7 CFU i.v.	10^8 CFU i.v.	10^9 CFU i.v.	10^4 CFU i.c.
2 h	Blood	4.88	5.47	>6.24	
	Brain	0	0	0	2.13
1 day	Blood	3.80	4.78	4.58	
	Brain	2.88	3.27	2.95	2.78
7 days	Blood	4.62	3.38	4.32	
	Brain	3.15[1]	3.88	4.0[1]	3.38[1]
14 days	Blood	2.56	2.65	4.88	
	Brain	4.30[1,2]	3.95[1]	4.18[1]	4.01[1,2]
28 days	Blood	<1.8	4.34	5.30	
	Brain	3.65[1]	4.56[1,2,3]	4.69[1,2]	4.51[1,2]
56 days	Blood	2.36	4.04	3.71	
	Brain	2.87	4.68[1,2,3]	4.69[1,2]	3.40

[a] [1], $P < 0.05$ compared with the number of bacteria in the brain at day 1; [2], $P < 0.05$ compared with the number of bacteria in the brain at day 7; [3], $P < 0.05$ compared with the number of bacteria in the brain at day 14.

groups of mice were given suspensions of 1.2×10^7, 1.2×10^8, or 1.2×10^9 organisms in 100 μl of HBSS by tail vein injection. Blood and brain were obtained from 2 h to 2 months after *M. avium* infection to determine the bacterial load and histopathologic changes. Mice infected by the i.v. route were compared with mice receiving 3×10^4 organisms by i.c. infection.

For blood culture, 0.05 ml of blood was drawn from the tail

vein and inoculated into BACTEC 12B radiometric medium (Johnson Laboratories, Towson, Md.). The number of bacteria present in the blood was determined by using the T100 method, as previously reported (3). For brain culture, mice were killed by intramuscular injection of ketamine (400 mg/kg) and xylazine (80 mg/kg), and the brain was removed and homogenized in 2 ml of Middlebrook 7H9 broth as previously described (18). Serial 10-fold dilutions of the homogenate were plated onto Middlebrook 7H11 agar supplemented with OADC. After incubation for 7 to 10 days at 37°C, the number of colonies was quantitated. For the histopathological tissue preparation, immediately after being killed, the mice were intracardially perfused with 30 ml of heparin solution (10 U/ml) followed by 60 ml of 4% paraformaldehyde. After subsequent fixation with 4% paraformaldehyde, the brain was embedded in paraffin, sectioned at 4 μm, and stained either with hematoxylin-eosin (HE) or by the Ziehl-Neelsen method.

Immunohistochemistry was carried out using paraffin preparations as described before (15, 16) with anti-CD4 and anti-CD8 antibodies (Pharmingen, San Diego, Calif.). Briefly, samples were deparaffinized and rehydrated, and the endogenous peroxidase was blocked with 3% H_2O_2 for 5 min. After washing, antigens were unmasked by treatment with 1 mM EDTA (pH 8) with heat until boiling. After washing, the sample was blocked with serum and then exposed to anti-CD8 (clone 53-5.8) or anti-CD4 (clone H129.19) antibodies followed by the biotinylated second antibody and the ABC reagent (Vector, Burlingame, Calif.). The number of positive cells was counted under the microscope by two individuals. As a control for staining, spleen tissues from infected mice were run in parallel.

In subsequent experiments, mice were infected with 6×10^9 bacteria by the i.v. route. From 4 to 11 mice were used for blood culture and 7 mice were used for brain culture at each time point between 2 h and 6 months. Histopathologic examination was performed during this period as well. In the exper-
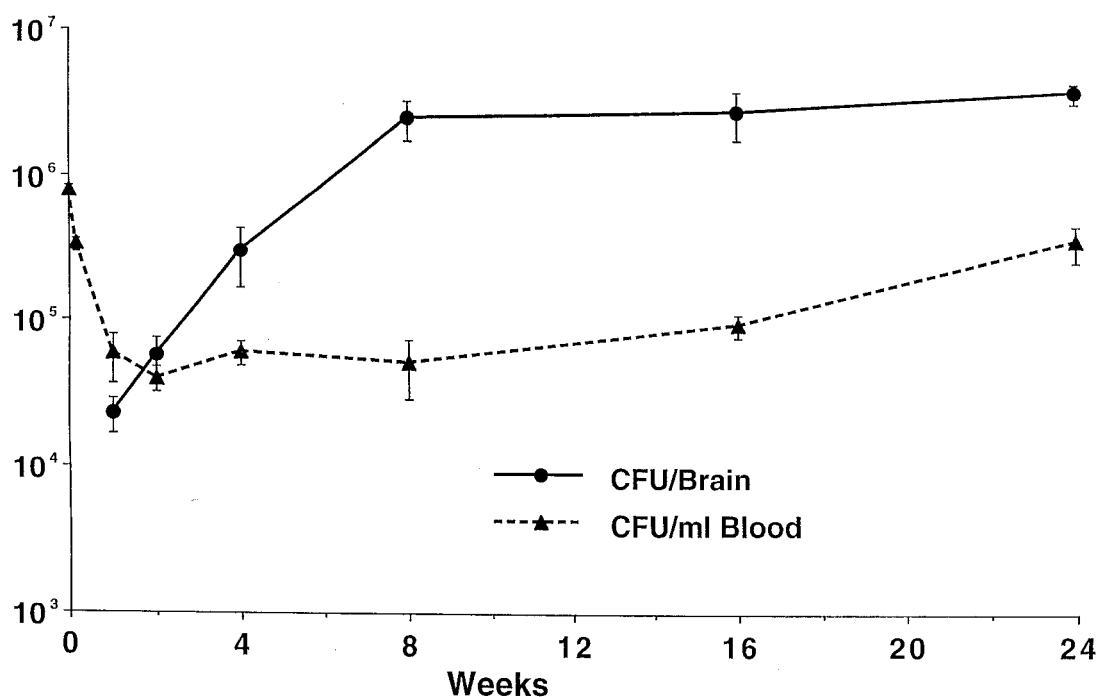

FIG. 1. Mice were given 6×10^9 CFU of *M. avium* 101 i.v. Four to 11 mice were used for blood culture and 3 to 7 mice were used for brain culture at each timepoint. Data are the mean CFU ± SEM. Mice had a significant increase in bacterial load in the brain within the first 2 months ($P = 0.0058$).

TABLE 2. Number of bacteria in the brain of mice
after i.c. inoculation

Day after infection	No. of bacteria/brain[a]		
	1.2×10^3 CFU	1.2×10^4 CFU	1.2×10^6 CFU
1	0	1.75×10^3	3.45×10^3
4	$4.2 \times 10^{2\ a}$	1.95×10^3	$3.3 \times 10^{4\ a}$
8	0	4.95×10^3	$6.38 \times 10^{4\ a}$
78	0	ND[b]	1.78×10^3

[a] $P < 0.05$ compared with the number of bacteria in the brain at day 1.
[b] ND, not done.

iments with CD18 KO mice, 3×10^8 bacteria were used to infect mice i.v. Ten mice were used per experimental group.

The results represent the mean ± the standard error of the mean (SEM). The significance of the results was determined by Student's *t* test and Fisher's exact test.

Mice tolerated *M. avium* infection very well when infected by either the i.v. or i.c. route. Except for a slight body weight loss observed at the end of the experiment, no mice died. No prominent movement impairment, convulsions, seizures, or gait disturbance was noted during 2 months of observation in the i.c.-infected mice or up to 6 months of observation in the i.v.-infected mice.

In mice given 1.2×10^7, 1.2×10^8, or 1.2×10^9 *M. avium* by the i.v. route, an early peak of bacteremia with magnitude related to the inoculum size could be detected 2 h after inoculation (Table 1). Sustained circulating levels of *M. avium* (10^4 CFU/ml) persisting for 2 months were observed in mice receiving 1.2×10^8 or more bacteria (Table 1). Similar results were seen in mice receiving 6×10^9 organisms and observed

for up to 6 months (Fig. 1). The number of bacteria in the brain did not change significantly from 8 weeks to 6 months after infection.

In the i.c.-infected mice, bacteria could only be recovered from the brain of mice that received $>10^3$ organisms. The number of bacteria recovered from the brain 1 day after infection was much smaller than the inoculum used (Table 2). However, the number of organisms increased progressively afterwards (Table 2) and reached a load similar to the number of bacteria injected at about 1 month postinfection, when marked meningoencephalitis could be observed microscopically (Fig. 2). In the mice given 1.2×10^8 organisms as well as in mice receiving greater numbers of bacteria i.v., the bacterial burden in the brain increased progressively during the first 2 months after infection (Table 1) and then remained constant until the termination of the study (Fig. 1).

In both mice receiving 3×10^8 CFU of *M. avium* i.v. or 3×10^4 CFU of *M. avium* i.c., inflammatory changes in the brain were not observed until 1 month after infection. Nonetheless, bacteria were recovered from the brain early after infection. In the i.c.-infected mice, marked meningoencephalitis with prominent granulomatous infiltration (especially around the basal cistern), perivascular lymphocytes, and macrophages cuffing were observed 1 month after infection (Fig. 2), and frank periventricular and choroid plexus infiltration were detected 2 months later. However, there were only a few acid-fast bacilli in these lesions, and no necrosis or giant cells were seen. In the i.v.-infected mice, low-grade inflammation with macrophages and T lymphocytes was the only change observed. Immunohistochemical analysis showed that $80 \pm 6\%$ (mean ± SEM) of the lymphocytes were CD8+ T cells and $9 \pm 3\%$ stained for CD4+ T cells. Focal meningeal infiltration as well as vasculitis and small aggregates of lymphocytes and macrophages in the
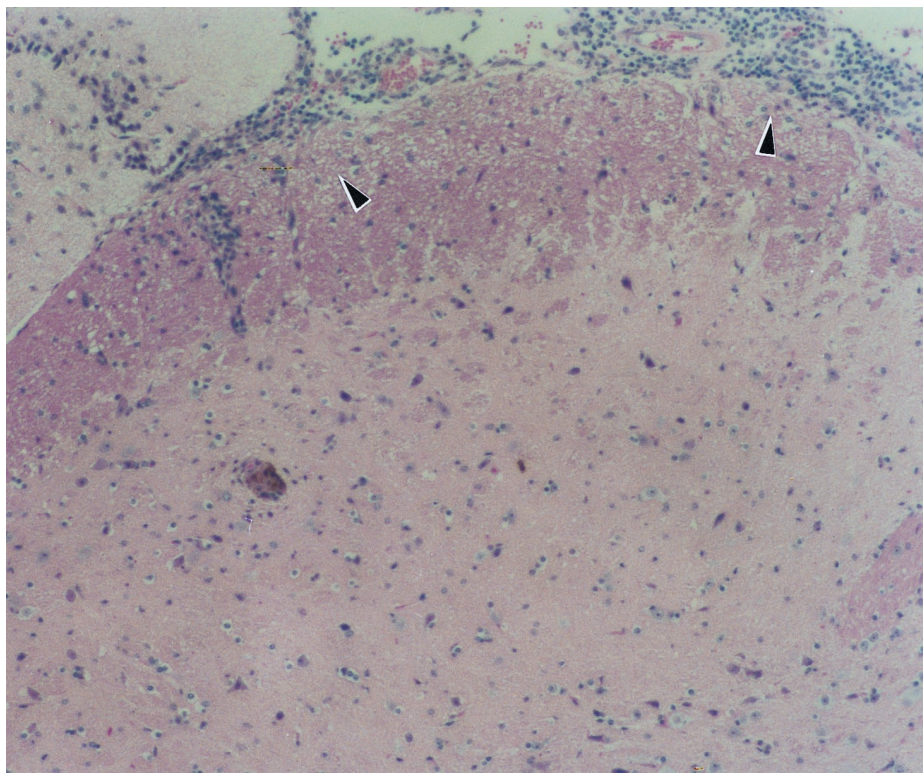

FIG. 2. Brain histopathology, showing intense infiltration of lymphocytes and macrophages in the optical chiasm 2 weeks after i.c. infection.
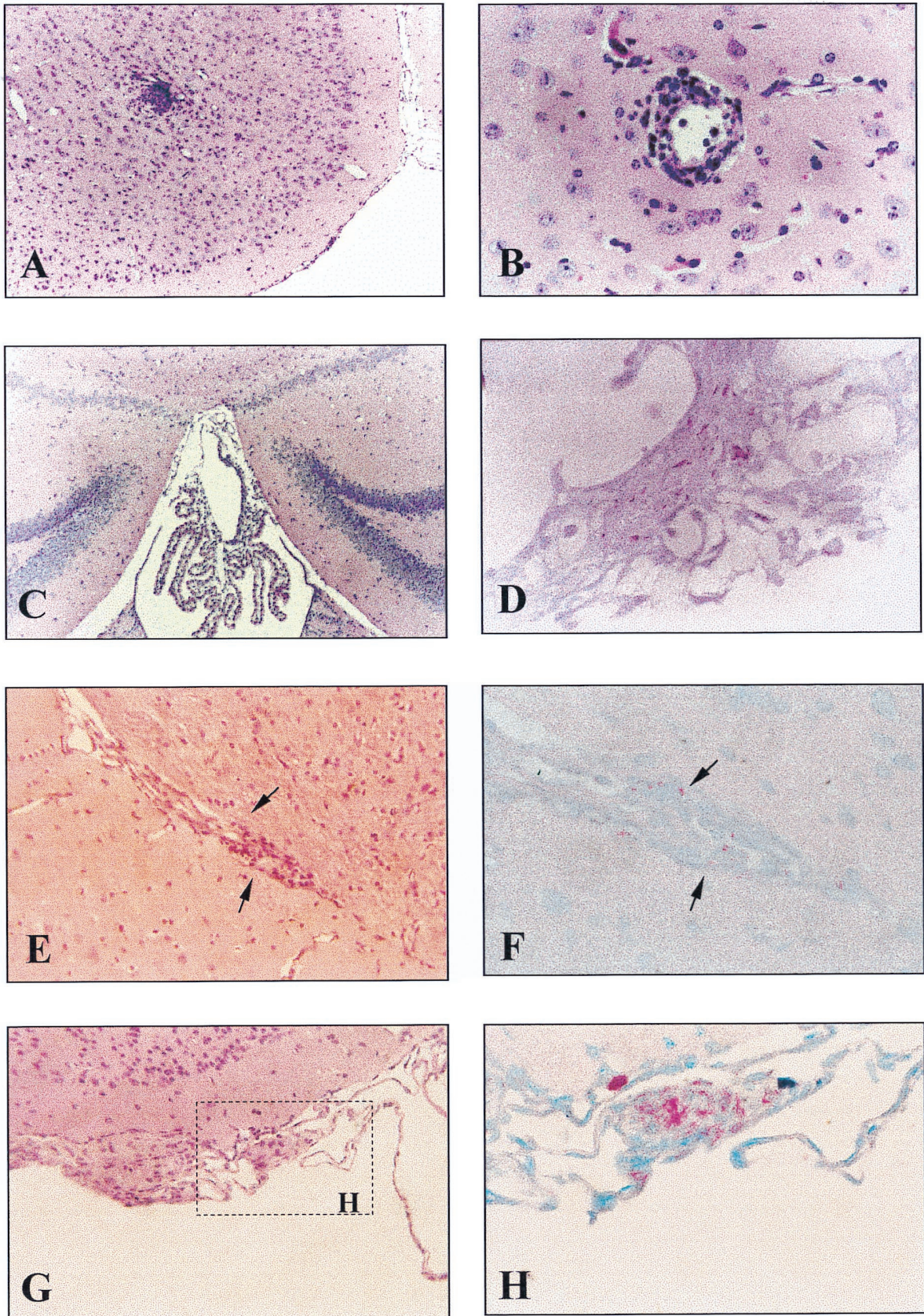
FIG. 3. Brain histopathology of mice receiving 3×10^8 CFU i.v. (A) At 1 month after inoculation, one nonnecrotizing granuloma was seen; HE strain. (B) Perivascular cuffing seen 2 months after inoculation. HE stain. (C) mild choroid plexus infiltration. HE stain. (D) acid-fast bacilli in the parenchyma of the choroid plexus. AFB stain. (E and F) At 4 months after infection there was cellular infiltration along the ventricle (E) (HE stain) and acid-fast bacilli were found in the lesion (F) (AFB stain). (G and H) At 6 months after inoculation, meningeal granuloma with foamy histiocytes was found (G) (HE stain) containing numerous acid-fast bacilli (H) (AFB stain). Magnifications: A and C, ×100; B, ×400; D, ×630; E and G, ×250; F and H, ×600.

TABLE 3. Comparison of the number of *M. avium* in the brains of wild-type and CD18 KO mice after i.v. infection[a]

Day postinfection	10^5 CFU/g of brain (mean ± SEM, n = 10)	
	Wild type	CD18 KO
1	1.2 ± 0.4	1.6 ± 0.2
7	2.4 ± 0.3	2.7 ± 0.3
14	3.5 ± 0.4	3.9 ± 0.1
28	3.3 ± 0.6	4.0 ± 0.5

[a] $P > 0.05$ for all the comparisons between number of bacteria in wild type and CD18 KO at each timepoint.

parenchyma could be observed 1 month after inoculation (Fig. 3). Mild choroid plexus infiltration accompanied by numerous acid-fast bacilli was seen in all the brains studied 2 months later (Fig. 3). Four months after infection, acid-fast bacilli could be easily found in the subarachnoid space. Aggregates of foamy histiocytes containing numerous acid-fast organisms were further identified 6 months after infection along the ventricle and meninges (Fig. 3).

To investigate whether transport within monocytes or neutrophils represented a mechanism of *M. avium* invasion of the CNS, we infected both C57BL and C57BL CD18^{−/−} KO mice i.v. and determined the number of bacteria in the brain at several timepoints after infection. As shown in Table 3, CD18^{−/−} KO mice, in which monocytes and neutrophils are significantly impaired in their ability to travel across the blood vessel wall, showed the same number of organisms in the brain as the C57BL wild-type mice.

We have analyzed the kinetics of CNS invasion by *M. avium* after i.v. infection. Our results suggest that *M. avium* infection of the CNS during AIDS is an underrecognized entity. We used strain 101, which is a well-characterized virulent strain of *M. avium* (3). Other strains, such as the virulent strain 724 (22), however, may prove to be more invasive of the CNS or trigger a greater inflammatory response than strain 101 and should be investigated in this model in the future.

In our system, the number of bacteria in the brain increases with the duration and level of bacteremia, which suggests that the duration and magnitude of bacteremia play an important role in the pathogenesis of *M. avium* brain disease, as has been recognized for acute bacterial meningitis caused by other organisms, such as *Streptococcus pneumoniae* and *Listeria monocytogenes* (4).

In contrast to the marked inflammatory response observed in i.c.-infected mice, i.v.-infected mice with the same bacterial burden in the brain developed only a mild inflammatory response. Why the intensity of the immune response is different when bacteria enter the CNS via different routes is not understood, but the trauma caused by i.c. administration (bringing defense cells to the site) in association with the infectious process may be responsible for the inflammation. In fact, patients with *M. avium* brain infection, often associated with bacteremia, can show heavy cellular infiltration and bacterial burden in the wall of the small bowel and lymph nodes, although the inflammatory changes in the CNS are often mild (11, 15).

Histopathologic changes with *M. avium* CNS infection have not been well defined, but in the reported cases poorly formed granulomas without central necrosis, perivascular cuffing, and mild focal cellular infiltration in the meninges were mentioned as well as the existence of the characteristic aggregates of foamy histiocytes containing an abundance of intracellular ba-

cilli (9, 11, 15). Likewise, our histopathologic findings in the brains of mice infected systemically with *M. avium* showed similar features, indicating that this murine model appears to be suitable for further pathophysiological study of *M. avium* brain infection.

Microscopically, acid-fast bacilli were present, especially in the parenchyma of the choroid plexus of i.v.-infected mice, suggesting that the choroid plexus may be an important route by which *M. avium* enters the neuraxes. The choroid plexuses are derived by invagination of the neuroepithelium and are therefore located within brain substance, although it shows continuity with the meninges (19). Despite this deviation and topography, the exceptionally high blood flow and lack of intercellular tight junctions in its thin fenestrated endothelium may serve as the preferable site for entry of pathogens into CNS. For instance, meningococcal meningitis is widely believed to begin in the choroid plexus, and a similar pathogenic sequence has been suggested for tuberculous meningitis, *Haemophilus influenzae* meningitis, *Escherichia coli* meningitis, and listerial meningoencephalitis (7, 20, 23, 24). Our data suggest that *M. avium* may penetrate the CNS by the choroid plexus with subsequent dissemination to the ventricular system and from there to the spinal fluid, meninges, and subarchoidal space. Furthermore, the results obtained with CD18 KO mice make it very unlikely that *M. avium* would enter the CNS within cells such as monocytes and neutrophils. In our model, the whole process takes approximately 4 to 6 months, and although a large number of bacteria can be seen in those above-mentioned areas of the brain, no apparent symptoms or signs can be observed in infected mice. It is possible that the mild inflammatory response associated with *M. avium* infection (16) with induction of low levels of tumor necrosis factor alpha and suppression of the release of chemokines such as interleukin-8 (21) might explain the near absence of symptoms. In fact, such a clinical course may explain the potentially underdiagnosed clinical entity in AIDS patients. Further studies addressing the cells and cytokines involved in the host response to CNS *M. avium* infection are under way.

Although nothing is known about the molecular mechanisms allowing *M. avium* to invade the CNS, our results suggest that bacteria might cross the blood-brain barrier by invading the epithelial cells in the choroidal plexus and not by crossing tight-junction endothelial cells. Other groups using SCID mice have noticed similar degrees of infection in the brain and absence of symptoms and signs (8).

Compared with the many well-developed acute bacterial meningitis models (25), chronic CNS infection models are not well established. In this study, we describe invasion of the CNS by *M. avium* via i.v. inoculation instead of direct i.c. injection, which resembles the natural course of human disease. This model may be useful in the investigation of the immunohistopathology cascade of NTBM brain infections.

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