Six cases of middle cerebral artery occlusion are presented in which the cellular changes accompanying descending degeneration of the lateral corticospinal tract were studied at different time points (5 days–10 years) following the insult. Microglia and perivascular cells were found to ingest large amounts of myelin degradation products, while expressing high levels of major histocompatibility complex (MHC) class II molecules. Activation of perivascular macrophages, as indicated by increased class II expression, lasted for many years and appeared to follow down-regulation of both phagocytic activity and class II expression on parenchymal microglia. TUNEL labeling was absent from both microglia and perivascular cells at all time points investigated. Indirect evidence is presented that microglia may transfer myelin degradation products to the perivascular space. Perivascular cells which express MHC class II molecules constitutively do not appear to leave the perivascular compartment in large numbers and could release myelin degradation products into the cerebrospinal fluid. The possible immunological consequences of these findings are discussed with respect to their possible relevance for antigen presentation and autoimmune central nervous system disease.
tans, i.e., in the perivascular space. The cells were termed 'perivascular cells' [21] and have recently found much attention as they are most likely involved in antigen presentation at the blood-brain interface [12, 16]. However, their role in the immunological changes associated with Wallerian degeneration in the spinal cord is poorly understood. We have studied the time course of expression of immunomolecules known to be associated with activated microglia/brain macrophages and perivascular cells in the human spinal cord undergoing pyramidal tract degeneration. Time points studied ranged from 5 days to 10 years following middle cerebral artery occlusion. A dramatic and long-lasting increase was observed in the number of major histocompatibility complex (MHC) class II-positive perivascular cells containing large amounts of myelin degradation products, raising the important question of their immunological relevance during Wallerian degeneration.

Materials and methods

Subjects

Six cases with a history of middle cerebral artery infarction (5 days, 6 weeks, 16 weeks, 3 years, 4 years and 10 years following middle cerebral artery occlusion) were obtained at the Institute of Neuropathology of the University of Munich. Detailed summaries of the case reports are given in Table 1.

Neuropathological examination

Brain and spinal cord tissue was fixed in 3.7% formaldehyde solution for at least 1 week at room temperature. Microscopic examination was carried out using 3-µm-thick paraffin sections taken from the relevant cortical areas, brain stem and spinal cord. Hematoxylin and eosin (H&E) and cresyl violet-Luxol fast blue were used as routine stainings. In addition, frozen sections of spinal cord (cases 1–5) and medulla oblongata (case 6) were stained with Sudan III.

For immunocytochemistry, paraffin sections were obtained from cervical, thoracic and lumbar spinal cord (cases 1–5) as well as medulla oblongata (case 6). Endogenous peroxidase activity was quenched in 7.5% H₂O₂ for 5 min. Following incubation in 0.01 M phosphate-buffered saline (PBS) for 15 min, sections were incubated in 1% rabbit normal serum for 30 min. Incubation with the following monoclonal antibodies was carried out at 4°C overnight (dilution 1:100 in PBS): CR3/43 (anti-MHC class II; Dako, M 775) [14], Ki-M1P (Seikagaku, no. 93401) [27], LC (Dako, M 701), UCHL1 (Dako, M 742), and L26 (Dako, M 0755).

Antibody binding was detected using biotinylated anti-mouse rabbit immunoglobulin (Dako, E 354, 1:400) and peroxidase-conjugated streptavidin (Dako, P 397; 1:1000). Visualization was carried out with 1 mg/ml 3,3’-diaminobenzidine (Dako, S 3000) and 0.05% H₂O₂ in 0.05 M TRIS-HCl, pH 7.6, containing 0.15 M NaCl.

Table 1 Case reports (a.m. ante mortem)

| Age (years) | Sex | Event of stroke a.m. | Clinical findings | Main autopsy findings | Cause of death |
|-------------|-----|---------------------|------------------|----------------------|---------------|
| Case 1 62 | f   | 5 days              | Cardiac insufficiency, bypass surgery 5 days a.m., intraoperative left middle cerebral artery occlusion, minimal therapy | Severe general arteriosclerosis, acute myocardial infarction, biventricular myocardial hypertrophy; thrombosis of right femoral and right jugular vein, paracentral pulmonary embolism, pulmonary edema | Cardiac failure caused by pulmonary embolism and myocardial infraction |
| Case 2 44 | m   | 6 weeks             | Acute left hemiplegia, right-sided leg-pronounced hemiparesis; cranial CT scanning: infarction of right middle cerebral artery and right basal ganglia hemorrhage; pneumothorax, staphylococcal sepsis | Recurrent paracentral and acute central pulmonary embolism, cor pulmonale, thrombosis of right and left femoral veins | Recurrent paracentral and acute central pulmonary embolism |
| Case 3 85 | f   | 16 weeks            | Right femoral neck fracture 5 months a.m.; myocardial infarction and left-sided cerebrovascular insult 4 months a.m.; total hip replacement, postoperative progressive cardiocirculatory failure | Severe general arteriosclerosis, arteriosclerotic heart disease; severe osteoporosis; pulmonary emphysema | Cardiac failure |
| Case 4 86 | m   | 3 years             | For 3 years left-sided hemiparesis and sensory disturbance after stroke, 1 day a.m. embolectomy in left superficial femoral artery, postoperative bradycardia and asystolia | Severe general arteriosclerosis, arteriosclerotic heart disease, old myocardial infarction; acute purulent bronchopneumonia; complete micronodular liver cirrhosis | Cardiocirculatory failure with acute bronchopneumonia |
| Case 5 66 | m   | 4 years             | Myocardial infarction 14 years a.m. right-sided stroke and left-sided hemiparesis 4 years a.m.; stenosing gastric cancer, cachexia; acute myocardial infarction during gastrectomy | Severe general arteriosclerosis, arteriosclerotic heart disease, gastric adenocarcinoma; pancreatic fibrosis | Cardiocirculatory failure |
| Case 6 70 | m   | 10 years            | Apoplexia followed by right-sided hemiplegia and aphasia 10 years a.m.; myocardial infarction, cardiac pulmonary oedema 18 days a.m.; sepsis | Severe general arteriosclerosis, myocardial infarction; acute bronchopneumonia; cholangitis | Cardiocirculatory failure, sepsis |
Quantitative image analysis

Quantitative evaluation of demyelination, MHC class II-positive cells and lipophages was performed using the image analysis software package Optimas 5.1 (Optimas Corporation, Seattle, Wash.). The right and left lateral corticospinal tracts were identified based on their anatomic location. For all stained sections to be analyzed, thresholds for the detection of specifically labeled cells were set individually using visual control. Perivascular and non-perivascular areas were selected and the respective tissue areas (0.062 mm²; ×40 objective) determined based on the average value of three independent measurements. The resulting percent areas were calculated and compared between the normal and the affected side. Independent measurements were performed for perivascular and non-perivascular class II-immunoreactive cellular profiles as well as Sudan III-stained and Luxol fast blue-positive cells. Areas of profiles were defined with minimum boundaries of 10 pixels (cresyl violet-Luxol fast blue) and 20 pixels (CR3/43, Sudan III).

Electron microscopy

Formalin-fixed tissue blocks taken from the spinal cord of case 5 (Table 1) were post-fixed for 3 weeks in a 3.7% formaldehyde/0.75% glutaraldehyde-buffered (0.1 M, pH 7.4) fixation solution. Vibratome sections (Oxford vibratome, Technical Products International, St. Louis, Mo.) were made and post-fixed for 24 h. After several washes in cacodylate buffer (0.1 M, pH 7.4), small (1 mm³) tissue blocks were cut and fixed in 1% Dalton’s osmium overnight. Subsequently, the blocks were processed for Araldite embedding. Thin sections were contrasted using uranyl acetate and lead citrate. Terminal transferase-mediated nick end-labeling (TUNEL) Nick end-labeling of double-stranded DNA breaks was performed as described [20]. In brief, following proteinase K treatment, de-waxed and rehydrated tissue sections were incubated at 37°C for 1 h in 1.6 µM biotin-16-dUTP (Boehringer Mannheim, Mannheim, Germany) and 0.08 U/µl terminal transferase (Boehringer Mannheim) in TdT buffer (3.0 mM TRIS, pH 7.2, 14 mM sodium cacodylate, 0.1 mM CoCl₂). TUNEL labeling was visualized using peroxidase-conjugated streptavidin and 3,3′-diaminobenzidine. Nuclei were counterstained with Nuclear Fast Red. Sections of tonsil and small intestine were used as positive controls in each series of labelings.

Results

Following occlusion of the middle cerebral artery, the pathological changes in the corresponding pyramidal tract ranged from visually nearly unaffected (5 days) to com-

Table 2 Summary of neuropathological findings

| Event of stroke a.m. | Age (years) | Brain weight (g) | Large arteries of the base of the brain | Coronal sections | Midbrain, brain stem and spinal cord |
|----------------------|-------------|------------------|----------------------------------------|-----------------|------------------------------------|
| Case 1 5 days        | 62          | 1380             | Slight arteriosclerotic changes, fresh blood clot in the left middle cerebral artery with luminal occlusion | Anemic necrosis stage I affecting the complete area of the left middle cerebral artery, midlineshift from left to right side, narrowing of the left lateral ventricle | Tentorial herniation with multiple midbrain hemorrhages and hemorrhages in the tegmentum pontis; spinal cord without visible pathological changes |
| Case 2 6 weeks       | 44          | 1580             | No pathological findings | Anemic necrosis stage I-II affecting the area of the right middle cerebral artery, blood clot involving parts of the right basal ganglia | Signs of raised intracranial pressure; beginning axonal degeneration and demyelination in the right pyramidal tract |
| Case 3 16 weeks      | 85          | 1270             | Severe arteriosclerosis | Necrosis stage II-III (4 mm) in the left capsula interna | Beginning axonal degeneration and myelin sheath damage in the left pyramidal tract; small necrosis stage II affecting the left nucleus proprius V, nucleus ambiguous and nucleus funiculi lateralis |
| Case 4 3 years       | 86          | 1200             | Severe arteriosclerosis | Cystic necrosis stage III (4 cm × 4 cm) involving parts of the right capsula interna and parts of the putamen; small necrosis stage II-III in the right occipital lobe | Marked axonal degeneration and demyelination in the right pyramidal tract |
| Case 5 4 years       | 66          | 1400             | Vertebral and basilar arteries with several arteriosclerosis, moderate arteriosclerosis of the internal carotid and middle cerebral arteries | Cystic necrosis stage III with complete destruction of the right capsula interna, putamen and globus pallidus | Severe axonal degeneration and myelin loss in the right pyramidal tract; cerebello-medullary herniation |
| Case 6 10 years      | 70          | 1050             | Moderate general arteriosclerosis, severe arteriosclerosis of the left internal carotid artery | Cystic necrosis stage III with complete destruction of the left caudate, putamen, and capsula interna, parts of the pallidum and lateral parts of the thalamus | Nearly complete axonal degeneration and myelin loss in the left pyramidal tract |
complete axonal degeneration and loss of myelin (after 10 years; Table 2). For quantitative evaluation of the different staining results, morphometric analysis was performed on the lateral corticospinal tract. While the percent area of

Fig. 1 A, B MHC class II immunoreactivity in the lateral corticospinal tract following infarction of the middle cerebral artery is prominent on perivascular macrophages and also present on some parenchymal cells (A case 4, B case 5). C Perivascular Sudan III staining of a blood vessel from the case shown in B (MHC major histocompatibility complex). A × 130; B, C × 70

Fig. 2 Quantification of MHC class II- (A) and Sudan III- (B) positive profiles, and of demyelinated tissue areas (C) in the lateral corticospinal tract between 5 days and 10 years following occlusion of the middle cerebral artery. Percent areas of stained profiles were determined in three representative visual fields (0.062 mm²) on the affected and unaffected side, respectively. Values are given as mean ± SD. Asterisks significantly different from non-perivascular labeling, $P < 0.05$; ○ significantly different from contralateral side, $P < 0.05$ (Mann and Whitney U-test). Numbers in parentheses indicate the survival time after stroke involving the middle cerebral artery (n.d. not determined)
demyelinated spinal fiber tracts did not exceed 20% up to 4 months after the insult (cases 1–3), demyelination exceeded 80% at 3 years (case 4) and approached 100% after 4 years (cases 5 and 6). Intense perivascular clustering of CR3/43-positive cells was observed in demyelinated tissue areas in cases 4 and 5 (Figs. 1, 2). This finding was statistically significant compared to non-perivascular and contralateral perivascular tissue areas ($P < 0.05$, Mann and Whitney U-test) (Fig. 2). As shown by electron microscopy, clustered cells met the morphological criteria of perivascular cells (Fig. 3) [10, 12]. The cells contained large numbers of lipid droplets, suggesting extended uptake and accumulation of myelin breakdown products in these cells over many years (Figs. 1, 2). A few macrophages with lipid droplets were also found in the adjacent meninges. At earlier stages of corticospinal tract degeneration, strong CR3/43 immunoreactivity of both brain macrophages and ramified microglia was also observed in parenchymal, i.e., nonperivascular tissue areas. The highest levels of perivascular and parenchymal class II expression was seen at 16 weeks after infarction (case 3, Fig. 2), but even 10 years after the ischemic injury, spinal cord labeling for MHC class II antigen had not returned to normal levels (case 6, Fig. 2). At the same time, up-regulation of perivascular class II expression was still detectable in the affected as well as in the unaffected lateral corticospinal tract. In cases 2–5, an increase in microglial activation was also seen on the contralateral side and in morphologically unaffected regions of the spinal cord. However, this labeling was much weaker than in the degenerating lateral pyramidal tract. Labeling of macrophages and microglia with Ki-M1P resulted in a slightly different overall labeling pattern since this antibody stains intracellular, lysosome-like structures (data not shown). In all cases only very few cells could be labeled for the LC, UCHL1, and L26 epitopes. Thus, there was no significant infiltration of lymphocytes. Apart from very few scattered cells, no TUNEL-positive structures were observed.

Fig. 3 Electron micrograph showing perivascular macrophages filled with lipid vacuoles (case 5, Tables 1, 2). The parenchymal basement membrane is marked by arrows. × 3600
Discussion

Our study demonstrates that there is a strong but slow and transient increase in the number of perivascular macrophages in tissue areas of the spinal cord affected by Wallerian degeneration of the lateral corticospinal tract following infarction of the middle cerebral artery. The cells contain large amounts of myelin degradation products and simultaneously express high levels of MHC class II antigen. We interpret the observed perivascular clustering of lipid-laden, MHC class II-positive cells as an indication for transport of myelin degradation products from the CNS parenchyma towards blood vessels in the degenerated tissue (Figs. 1, 2) [7, 8]. This view is in line with the observation that the staining for lipids became stronger in perivascular macrophages with increasing duration of the degenerative process and that it was most pronounced when the largest number of MHC class II-positive macrophages had accumulated in the perivascular space (Fig. 3). The perivascular macrophages described in this study most likely derive from a population of resident cells of the perivascular space termed perivascular cells [10, 12, 13, 18]. Perivascular cells are physiologically renewed from the bone marrow in the adult [16]. Although there is little information on their life cycle, perivascular cells have been suggested to develop into microglia under certain conditions [37]. However, turnover of perivascular CNS macrophages is slow and trafficking of their precursors through the blood-brain interface seems limited [34]. Furthermore, it remains unknown whether perivascular cells actually reenter the vasculature upon completion of their tasks which are generally considered phagocytosis and clearance of cellular debris from the CNS [21, 25].

There are different possibilities to explain the increased number of perivascular lipophages around blood vessels during late stages of Wallerian degeneration. It is conceivable that ‘resident’ perivascular cells can undergo mitosis before or after incorporating myelin degradation products. However, experimental studies on the facial nucleus of adult rodents suggest that these cells are largely post-mitotic even in their activated state [11]. Alternatively, the cells may be principally able to enter the circulation or migrate to the meninges, but lose this capacity after the incorporation of myelin degradation products. The latter possibility is attractive from a teleological point of view since perivascular ‘capture’ of CNS autoantigen during the acute phase of demyelination could represent a protective mechanism against autoimmunization. A third explanation would be that parenchymal microglia take temporary residence in the perivascular space after changing their phenotype into that of perivascular cells. However, there is no evidence to support this hypothesis. Answers to these questions are potentially of great immunological relevance as cells of the CNS perivascular space can gain direct access to the peripheral immune system [26]. Ten years after the insult, the number of lipid-containing cells and the perivascular expression of MHC class II molecules had reached almost normal levels and most myelin debris which is transformed into lipid droplets [7] had been cleared from the parenchyma. The number of microglia was also comparable to control levels. Based on our negative results using the TUNEL technique, we do not believe that apoptosis contributed significantly to the observed decrease in the number of lipid-laden perivascular cells. Similarly, Jones et al. [17] could show that apoptosis does not represent a major mechanism in the population control of microglial cells in vivo. In view of these findings, and since microglial cells are functionally deficient with respect to myelin removal [30], we believe that at least some of the perivascular lipophages could have directly entered the bloodstream or left the CNS via the meninges.

Phagocytosis is one of the strongest stimuli for microglial cells to express MHC class II molecules which are of crucial importance for antigen-dependent T cell responses [3, 4]. It has been previously demonstrated that sites of direct and indirect brain injury acquire a predisposition for the development of autoimmune inflammatory lesions [19, 24]. Even in the absence of breakdown of the blood-brain barrier [15, 29], autoimmune encephalomyelitis lesions can be targeted to CNS tissue undergoing Wallerian degeneration [19]. However, Wallerian degeneration is not normally followed by autoimmune attack. Thus, the CNS must be somehow protected against unwanted presentation of myelin-associated antigens to T lymphocytes [36]. Recent studies have shown that in addition to MHC class II molecules, co-stimulatory factors such as B7 are required to confer complete antigen-presenting capacity to MHC class II expressing cells, which are then able to stimulate a proliferative T cell response [5, 35]. Since the expression of co-stimulatory molecules has been described in multiple sclerosis lesions but not in neurodegenerative conditions [1, 5], we speculate that co-stimulatory factors may be absent from lipophages during Wallerian degeneration and that antigen presentation, if it occurs, may lead to T cell anergy rather than proliferation [9, 32]. Clearly, secondary rather than primary T cell responses should be considered in this context [33]. In the light of this hypothesis, the very slow breakdown of CNS myelin and the associated expression of class II molecules may confer a biological advantage and help to maintain the immune privilege of the CNS. Similarly, the well-established low threshold of microglia and perivascular cells for the up-regulation of MHC class II molecules could serve a protective function.

Acknowledgements The authors would like to thank A. Henn and D. Büringer for excellent technical assistance.

References

1. Banati RB, Graeber MB (1994) Surveillance, intervention and cytotoxicity: is there a protective role of microglia? Dev Neurosci 16: 114–127
2. Brück W, Brück Y, Maruschak B, Friede RL (1995) Mechanisms of macrophage recruitment in Wallerian degeneration. Acta Neuropathol 89: 363–367
3. Cash E, Rott O (1994) Microglial cells qualify as the stimulators of unprimed CD4+ and CD8+ T lymphocytes in the central nervous system. Clin Exp Immunol 98: 313–318
4. Cash E, Zhang Y, Rott O (1993) Microglia present myelin antigens to T cells after phagocytosis of oligodendrocytes. Cell Immunol 147: 129–138
5. De Simone R, Giampaolo A, Giometto B, Gallo P, Levi G, Peschle C, Aloisi F (1995) The costimulatory molecule B7 is expressed on human microglia in culture and in multiple sclerosis. J Neurophilopat Exp Neurol 54: 175–187
6. Franson P (1985) Quantitative electron microscopic observations on the non-neuronal cells and lipid droplets in the posterior funiculus of the cat after dorsal rhizotomy. J Comp Neurol 231: 490–500
7. Franson P, Ronnevi L-O (1984) Myelin breakdown and elimination in the posterior funiculus of the adult cat after dorsal rhizotomy: a light and electron microscopic qualitative and quantitative study. J Comp Neurol 223: 138–151
8. Franson P, Ronnevi L-O (1989) Myelin breakdown in the posterior funiculus of the kitten after dorsal rhizotomy: a qualitative and quantitative light and electron microscopic study. Anat Embryol (Berl) 180: 273–280
9. Gimmi CD, Freeman GJ, Grissen JG, Gray G, Nadler LM (1993) Human T-cell clonal anergy is induced by antigen presentation in the absence of B7 costimulation. J Natl Acad Sci USA 90: 6586–6590
10. Graeber MB, Streit WJ (1990) Perivascular microglia defined. Trends Neurosci 13: 366
11. Graeber MB, Streit WJ, Kreutzberg GW (1989) Formation of microglia-derived brain macrophages is blocked by adriamycin. Acta Neuropathol 78: 348–358
12. Graeber MB, Streit WJ, Kreutzberg GW (1991) Towards an immunological definition of the brain-blood barrier: significance of MHC class II positive perivascular cells. In: Yonezawa T (ed) Proceedings of the Xth International Congress of Neurology, Satellite Symposium on Demyelination, Mechanisms and Background. Neuropathology. Japanese Society for Neuropathology, Kyoto, pp 74–79
13. Graeber MB, Streit WJ, Büringer D, Sparks DL, Kreutzberg GW (1992) Ultrastructural location of major histocompatibility complex (MHC) class II-positive perivasculary cells in histologically normal brain. J Neuropathol Exp Neurol 51: 303–311
14. Graeber MB, Bise K, Mehrain P (1994) CR3/43, a marker for activated human microglia: application to diagnostic neuropathology. Neuropathol Appl Neuropathol 20: 406–408
15. Griffin JW, George R, Lobato C, Tyor WR, Yan LC, Glass JD (1992) Macrophage responses and myelin clearance during Wallerian degeneration: relevance to immune-mediated demyelination. J Neuroimmunol 40: 153–161
16. Hickey WF, Vass K, Lassman H (1992) Bone marrow-derived elements in the central nervous system -- an immunohistochemical and ultrastructural survey of rat chimeras. J Neuropathol Exp Neurol 51: 246–256
17. Jones LL, Banati R, Graeber MB, Bonfanti L, Raivich G, Kreutzberg GW (1997) Population control of microglia: does apoptosis play a role? J Neurocytol (in press)
18. Kida S, Steart PV, Zhang ET, Weller RO (1993) Perivascular cells act as scavengers in the cerebral perivascular spaces and remain distinct from pericytes, microglia and macrophages. Acta Neuropathol 85: 646–652
19. Konno H, Yamamoto T, Suzuki H, Yamamoto H, Iwasaki Y, Ohzora Y, Terunuma H, Harata N (1990) Targeting of adoptively transferred experimental allergic encephalitis lesion at the sites of Wallerian degeneration. Acta Neuropathol 80: 521–526
20. Kösel S, Egesenberger R, Etzen U von, Mehrain P, Graeber MB (1997) On the question of apoptosis in the parkinsonian substantia nigra. Acta Neuropathol 93: 105–108
21. Kreutzberg GW, Blakemore WF, Graeber MB (1997) Cellular pathology of the central nervous system. In: Graham DI, Lantos PL (eds) Greenfield’s neuropathology, 6th edn. Edward Arnold, London, pp 85–156
22. Lassman H, Zimprich F, Vass K, Hickey WF (1991) Microglial cells are a component of the perivascular glia limitans.
23. Ludwin SK (1990) Phagocytosis in the rat optic nerve following Wallerian degeneration. Acta Neuropathol 80: 266–273
24. Machlen J, Olsson T, Zachau A, Klarkeskog L, Kristensson K (1989) Local enhancement of major histocompatibility complex (MHC) class I and II expression and cell infiltration in experimental allergic encephalomyelitis around axotomized motor neurons. J Neuroimmunol 23: 125–132
25. Mato M, Okawara S, Mato TK, Namiki T (1985) An attempt to differentiate further between microglia and fluorescent granular perithelial (FGP) cells by their capacity to incorporate exogenous protein. Am J Pathol 172: 125–140
26. Ofenheim M (1978) Mononuclear phagocytes in the central nervous system. Springer, Berlin Heidelberg, pp 1–173
27. Paulus W, Ruggendorf W, Kirchner T (1992) Ki-M1P as a marker for microglia and brain macrophages in routinely processed human tissues. Acta Neuropathol 84: 538–544
28. Penfield W (1925) Microglia and the process of phagocytosis in gliomas. J Pathol 1: 77–97
29. Rao K, Lund RD (1993) Optic nerve degeneration induces the expression of MHC antigens in the rat visual system. J Comp Neurol 336: 613–627
30. Reichert F, Rotschenker S (1996) Deficient activation of microglia during optic nerve degeneration. J Neuroimmunol 70: 153–161
31. Schroeter M, Jander S, Huitinga I, Witte OW, Stoll G (1997) Phagocytic response in photochemically induced infarction of rat cerebral-cortex – the role of resident microglia. Stroke 28: 382–386
32. Schwartz RH (1990) A cell culture model for T lymphocyte clonal anergy. Science 248: 1349–1356
33. Talbot PJ, Paquette JS, Ciurli C, Antel JP, Ouellet F (1996) Myelin basic protein and human coronavirus 229E cross-reactive T cells in multiple sclerosis. Ann Neurol 39: 233–240
34. Unger ER, Sung JH, Manivel JC, Chenggis ML, Blazar BR, Krivit W (1993) Male donor-derived cells in the brain of female--mismatched bone marrow transplant recipients: a Y-chromosome specific in situ hybridization study. J Neuropathol Exp Neurol 52: 460–470
35. Van Seventer GA, Shimizu Y, Horgan KJ, Shaw S (1990) The LFA-1 ligand ICAM-1 provides an important costimulatory signal for T cell receptor-mediated activation of resting T cells. J Immunol 144: 4579–4586
36. Wecker H, Linnington C, Lassmann H, Meyerermann R (1986) Cellular immune reactivity within the CNS. Trends Neurosci 9: 271–277
37. Wisniewski HM, Weigel J (1993) Migration of perivascular cells into the neuropil and their involvement in beta-amyloid plaque formation. Acta Neuropathol 85: 586–595