Acta Neurochir (Wien) (1997) 139: 619–624

Acta Neurochirurgica

Different Release of Cytokines into the Cerebrospinal Fluid Following Surgery for Intra- and Extra-axial Brain Tumours

C. Woiciechowsky[1], K. Asadullah[2], D. Nestler[1], F. Glöckner[1], P. N. Robinson[3], H.-D. Volk[4], S. Vogel[1], and W. R. Lanksch[1]

Department of [1] Neurosurgery, Virchow-Klinikum, Departments of [2] Dermatology, and [3] Paediatrics, and Institute of [4] Medical Immunology, Charité, Humboldt University Medical School, Berlin, Federal Republic of Germany

Summary

To elucidate the role of cytokines in brain repair processes and in local inflammation after neurosurgical procedures, cerebrospinal fluid (CSF) samples from 8 patients with intra-axial tumours and 8 patients with extra-axial tumours were analysed for interleukin (IL)-1beta, IL-1 receptor antagonist (IL-1ra), IL-6, IL-8, IL-10, and tumour necrosis factor (TNF)-alpha at the beginning and after surgery. Levels of IL-6 and IL-8 increased dramatically in all patients just hours after surgery and fell during subsequent days. IL-1beta was found only in low amounts in the CSF of both patient groups. Other cytokines demonstrated different courses. In patients with intra-axial tumours IL-1ra peaked two to four hours after surgery with a subsequent decrease. In patients with extra-axial tumours there was a continuous low-level IL-1ra release into the CSF without a peak. TNF-alpha was not present in detectable levels in the CSF after surgery for extra-axial tumours but was found to peak two to four hours after surgery for intra-axial tumours. IL-10 was detected in the CSF of both patient groups, but a higher peak was seen after surgery for extra-axial tumours. These results suggest different requirements for the cytokine response and an involvement of different cell types in cytokine release. However, the analysis of the CSF from both patient groups showed no differences in cell counts and populations, with a mild pleocytosis being present in both patient groups after surgery. Therefore, we conclude that after surgery for extra-axial tumours cytokines were predominately produced by non-immune cells stimulated through hypoxia or mechanical irritation. After surgery for intra-axial tumours with a significant brain injury immune cells – activated by necrotic material – seem to be involved in the process of cytokine synthesis. In these cases an additional IL-1ra and TNF-alpha peak was found and these cytokines may be markers for cerebral injury.

Keywords: Cytokines; brain tumours; neurosurgery; cerebrospinal fluid; brain injury.

Introduction

Cytokines are a heterogeneous group of biologically highly effective polypeptides released by different cells in response to endogenous and exogenous stimuli. These mediators have autocrine, paracrine and endocrine capacities and pleiotropic regulatory effects on haematopoietic and many other cell types which participate in host defence and repair processes. The biological activities of cytokines are not developed by the release of a single cytokine but by the occurrence of a complex cytokine network.

Several studies have been performed to determine the importance of cytokines in various cerebral processes. Cytokines with a regulatory role in immune function may also mediate inflammation associated with brain injury and induce brain oedema as well as repair processes [11, 22, 23, 35]. The cytokines predominantly may derive from immune cells and microglia [12, 19, 21, 37]. However, astrocytes and endothelial cells are also capable of producing pro-inflammatory cytokines such as IL-1beta, IL-6, IL-8, and TNF-alpha [1, 8, 20, 22, 23, 36, 40]. Moreover, a number of studies showed that primary brain tumours can release pro- and anti-inflammatory cytokines in vivo and in vitro, especially IL-1beta, IL-6, TNF-alpha, TGF-beta, IL-10, and IL-1ra with various local and systemic effects (see reference [40] for review) [10, 15, 25, 26, 36, 37, 40]. In order to achieve a better understanding of actions of cytokines under natural conditions in response to brain injury, it is necessary to analyse not only one cytokine but the cytokine network.

We have recently demonstrated that neurosurgery can induce signs of local inflammation with a systemic immunosuppression and an increased risk of infection [2, 3, 42]. The aim of the present study was to determine the cytokine pattern in the CSF following

different neurosurgical procedures, in order to further complete the knowledge about inflammatory response to distinct CNS trauma. In order to characterise the cytokine network, pro-inflammatory cytokines like IL-1beta, IL-6, IL-8, and TNF-alpha as well as anti-inflammatory cytokines like IL-10 and IL-1ra have been selected for detection. The measurement of the cytokines was started during surgery to discover also early and temporary post-traumatic peaks, impossible to determine in accidental head injury or chronic neurological patients. Moreover, the kinetics of cytokines in the CSF after surgery for extra- and intra-axial tumours were compared, because cytokine release in different anatomical compartments after different kinds of surgical trauma should reflect involvement of different cell populations with distinct cytokine patterns. Only surgery for intra-axial tumours is associated with a significant brain lesion resulting in a more pronounced activation of neural as well as immune cells by necrotic cell components and hypoxia. This may be considered as a model for brain injury and help to detect cytokines suggested to be parameters for brain tissue damage. Moreover, it was interesting to study how immune and neural cells act together in the cytokine response to brain injury, compared with the process of local cytokine release after surgery for extra-axial tumours.

Patients and Methods

The group studied consisted of 8 patients undergoing surgery for intra-axial tumours adjacent to the ventricular system (2 neurocytomas, 3 glioblastomas, 2 oligodendrogliomas, and 1 astrocytoma) and 8 patients with extra-axial tumours (4 meningiomas and 4 neurinomas) at the Charité University Medical School. All tumours were macroscopically totally removed and the postoperative enhanced CT scans showed no residual tumour. All patients received the identical peri-operative antibiotic prophylaxis (teicoplanin 6 mg/kg) and dexamethasone (4 mg 4 times daily initially, followed by a reduced dose over the next few days). Anti-epileptics (phenytoin) were only given when there was a history of seizures. There were no relevant differences in the age, sex ratio, duration of surgery, use of anaesthetic agents and blood transfusion between the patient groups.

For the study CSF samples were collected from the patients at the beginning of surgery, 2 to 4 hours after surgery, and 1, 2, and 4 days postoperatively. The samples were obtained from a ventricular drain which had been placed during surgery either because the ventricular system was opened or because there were pre-operative symptoms of increased intracranial pressure. The samples were immediately centrifuged and supernatants were stored at –80 °C. The cytokine levels were analysed using the following commercial enzyme-linked-immuno-assay (ELISA) kits: human IL-1beta, IL-6, IL-8, IL-1ra (Quantikine®, DPC, Bad Nauheim, Germany), IL-10 (Cytoscreen®, Laboserv, Giessen, Germany), and TNF-alpha (Medgenix Diagnostics, Ratingen, Germany). All CSF samples were subjected to cell counts.

Results

There were dramatically elevated levels of IL-6 and IL-8 in the CSF in all patients two to four hours after surgery compared with the value at the beginning of surgery (Figs. 1 and 2) with no significant differences between both patient groups. In contrast, IL-1beta was only present in low amounts, with a maximum two to four hours after surgery, without significant difference compared with the value at the beginning of surgery and without differences between both patient groups. The mean ± standard error of the mean (SEM) of IL-1beta in the CSF was two to four hours

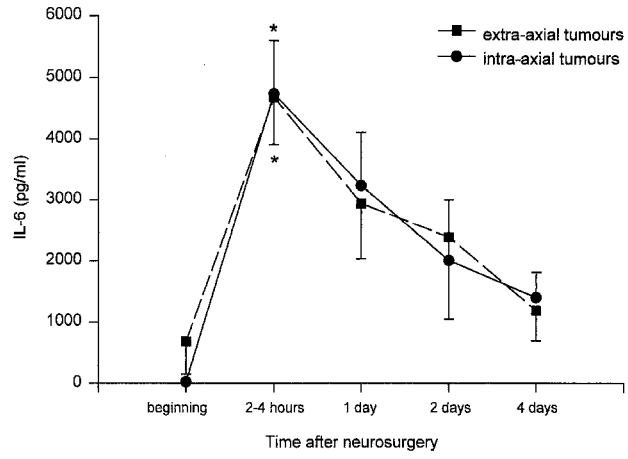

Fig. 1. Concentrations of IL-6 in the CSF before and after surgery for intra- and extra-axial tumours. Results are shown as mean ± SEM. *$p < 0.05$, compared with the value at the beginning of surgery, Wilcoxon Signed Rank Test

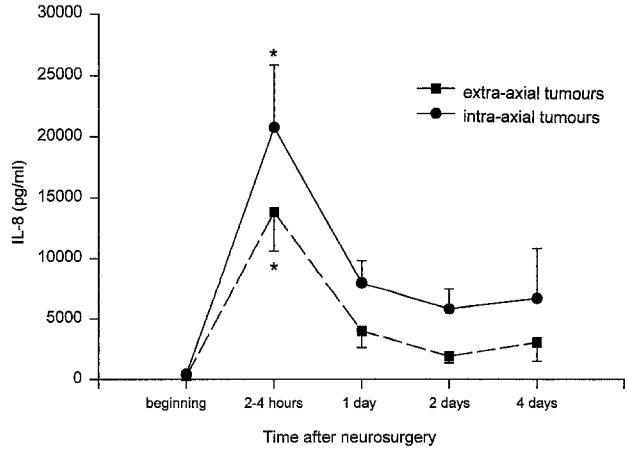

Fig. 2. Concentrations of IL-8 in the CSF after surgery for intra- and extra-axial tumours. Results are shown as mean ± SEM. *$p < 0.05$, compared with the value at the beginning of surgery, Wilcoxon Signed Rank Test

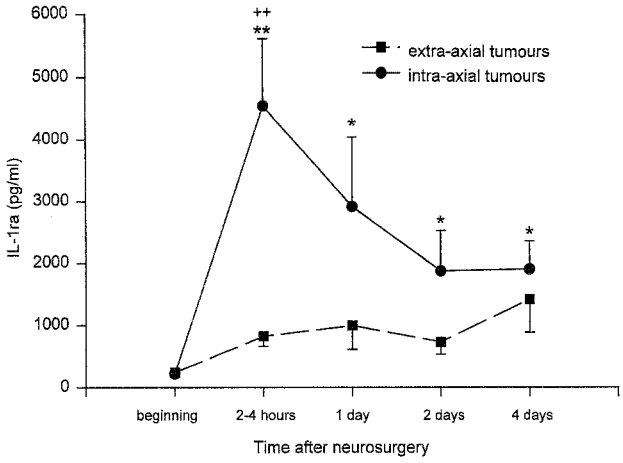

Fig. 3. Concentrations of IL-1ra in the CSF after surgery for intra- and extra-axial tumours. Results are shown as mean ± SEM. **p < 0.01, *p < 0.05 compared with the value at the beginning of surgery, Wilcoxon Signed Rank Test. ++p < 0.01 compared with the value of patients with extra-axial tumours at the same time point, Mann-Whitney Rank Sum Test

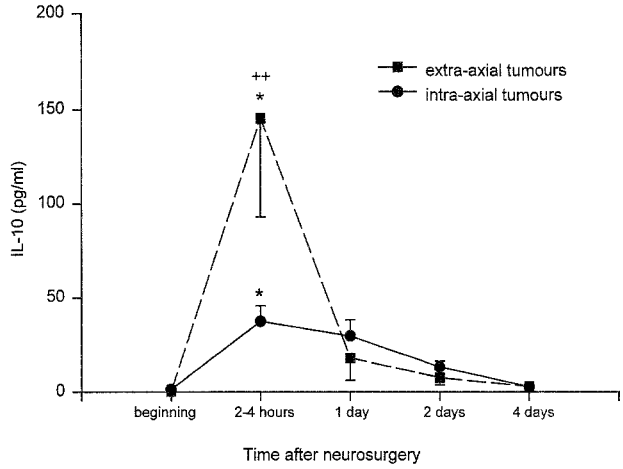

Fig. 5. Concentrations of IL-10 in the CSF after surgery for intra- and extra-axial tumours. Results are shown as mean ± SEM. *p < 0.05, compared with the value at the beginning of surgery, Wilcoxon Signed Rank Test. ++p < 0.01 compared with the value of patients with extra-axial tumours at the same time point, Mann-Whitney Rank Sum Test

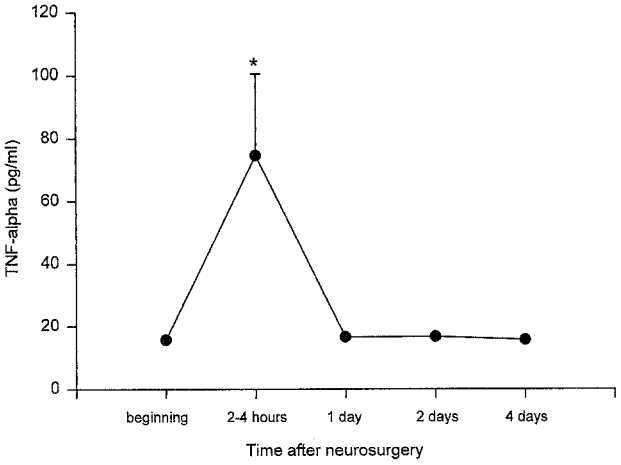

Fig. 4. Concentrations of TNF-alpha in the CSF before and after surgery for intra-axial tumours. Results are shown as mean ± SEM. *p < 0.05, compared with the value at the beginning of surgery, Wilcoxon Signed Rank Test

after surgery in patients with intra-axial tumours 6.2 ± 1.8 pg/ml and 7.9 ± 2.4 pg/ml in patients with extra-axial tumours, respectively.

Other cytokines demonstrated different levels at the selected times of sampling in the two patient groups. In patients with intra-axial tumours there were significantly elevated IL-1ra levels in the CSF two to four hours after surgery ($p < 0.01$), and 1, 2, and 4 days after surgery ($p < 0.05$, Wilcoxon Signed Rank Test) compared with the value at the beginning of surgery (Fig. 3). After surgery for extra-axial tumours there was a continuous low IL-1ra release into the CSF without a peak (Fig. 3). The differences were statistically significant in the two patient groups two to four hours after surgery ($p < 0.01$, Mann-Whitney Rank Sum Test). TNF-alpha was not found in the CSF after surgery for extra-axial tumours, but there was a significant increase ($p < 0.05$, Wilcoxon Signed Rank Test) two to four hours after surgery for intra-axial tumours compared with the value at the beginning of surgery (Fig. 4). IL-10 was found in CSF after surgery of both patient groups. However, there was a significantly ($p < 0.05$, Mann-Whitney Rank Sum Test) higher release two to four hours after surgery for extra-axial tumours compared with the value of patients with intra-axial tumours (Fig. 5).

The mean ± SEM of CSF cells two to four hours after surgery was 50.2 ± 15.6 Mpt/l in extra-axial tumours and 55.4 ± 11.9 Mpt/l in intra-axial tumours, respectively. There were no statistically significant differences between the groups.

Discussion

Cytokines are produced in the CSF in different situations and different cells may be involved in this process. Immune cells are the main source of cytokines, but in several conditions other cells may also release cytokines [2, 11, 12, 16, 19, 22, 23, 30, 33, 36, 40]. Astrocytes can produce IL-1beta, IL-6, IL-8, and TNF-alpha and these cytokines are considered to stimulate brain repair processes and astroglial scar-

ring [1, 11, 22, 23, 33]. Additionally, primary brain tumours are also able to produce cytokines which may in turn lead to local and systemic immunological effects [6, 9, 10, 15, 20, 25, 26, 34, 37, 40]. Therefore, the complex pattern of cytokines measured in the CSF after different surgical procedures demonstrates the response of different cells to an exogenous/endogenous stimulus.

In the present study we found a cytokine pattern indicating a local pro- and anti-inflammatory response early after neurosurgery in both patient groups. Interestingly, neurosurgical procedures with only minor injury to the brain tissue led to a high release of IL-6, IL-8, IL-10 into the CSF, but low IL-1beta and IL-1ra and no detectable TNF-alpha synthesis at all. In contrast, after surgery for intra-axial tumours associated with a significant brain tissue injury, high levels of IL-1ra and TNF-alpha were found in addition to the elevation of IL-6, IL-8, and IL-10. The different cytokine elaboration pattern in the two patient groups suggests the activation of distinct cell populations and/or different mechanisms of cell stimulation.

How can the demonstrated phenomena be explained? In several studies it has been shown that bacterial endotoxin induces an initial burst of pro-inflammatory cytokine synthesis in peripheral blood monocytes via CD 14 pathway with a release of TNF-alpha and IL-1beta, followed by IL-6 and IL-8. Subsequently, significant amounts of IL-10 and IL-1ra occur, limiting the expression and action of the pro-inflammatory cytokines [5, 7, 24, 41]. Blocking of TNF-alpha abolishes IL-6 and IL-8 release, and decreases IL-10 and IL-1ra production suggesting the important role of this pro-inflammatory key cytokine. Moreover, TNF-alpha is able to upregulate IL-6 and IL-8 secretion in non-immune cells such as endothelial cells, fibroblasts and astrocytes [1, 8, 16, 20, 39]. TNF-alpha and IL-1beta release is down-regulated within few hours following stimulation, whereas IL-10 secretion persists for 24–48 hours and IL-6 and IL-8 even for days [31].

Other stimuli like bacterial superantigen (SEB), complete bacteria, living or dying cells and 4-phorbol-12-myristate-13-acetate (PMA) induce a similar pattern of cytokine release. In contrast, phagocytosis of necrotic particles, adherence to surfaces as well as mild hypoxia result in a quite different cytokine pattern with a relative low level of TNF-alpha and IL-1beta, but high levels of IL-6 and IL-8. Moreover, hypoxia and bacterial endotoxin activate non-immune cells to release cytokines, particularly IL-6 and IL8, whereas TNF-alpha and IL-1beta are hardly detectable [14, 18, 43]. Monocytic IL-10 is upregulated in response to bacterial endotoxin and TNF-alpha [7, 24]. However, increase of intracellular cAMP resulting from action of prostaglandins or stress mediators also up-regulates IL-10 expression [24, 29]. These experimental data can be transposed to the in vivo situation. In fact, early gram negative sepsis is associated with elevated plasma levels of TNF-alpha, IL-1beta, IL-6, IL-8 as well as IL-10 and IL-1ra resulting from direct stimulation of monocytes/macrophages by endotoxin [31]. Late sepsis and sterile trauma (polytrauma, major abdominal and chest surgery) are associated with high circulating concentrations of IL-6, IL-8, and IL-10, but mainly undetectable concentrations of TNF-alpha and IL-1beta [13]. The cellular source of IL-6 and IL-8 in traumatic patients are probably non-immune cells (ischaemic endothelial cells, fibroblasts). IL-10 in these patients is presumably released by stress mediator-activated monocytes/macrophages [24, 29]. Furthermore, elevated IL-1ra levels were seen in plasma after major surgical interventions and may be a sensitive marker for tissue damage. It was supposed that IL-1ra released following surgery is produced by tissue macrophages in the operative field in response to necrotic cell components and subsequently enters the peripheral circulation [27, 28].

On the basis of these in vitro and in vivo observations we may speculate about the distinct cytokine pattern in our neurosurgical patients. High levels of IL-6, IL-8, and IL-10 but low concentrations of TNF-alpha, IL-1beta and IL-1ra in the CSF of patients after surgery for extra-axial tumours suggest the activation of non-immune cells. We suppose that the cellular source of IL-6 and IL-8 may be astrocytes and endothelial cells. Stimulation of these cells may result from local hypoxia and mechanical irritation of the brain tissue surrounding the operative field with only low occurrence of necrotic cells. However, immune cells – not stimulated via CD 14 pathway – can also contribute to the release of IL-6 and IL-8. The increased levels of IL-10 may arise from a TNF-alpha independent induction resulting from local rise of stress mediators and subsequently increase of intracellular cAMP, because there was a significantly higher IL-10 peak in the CSF after surgery for extra-axial tumours, where TNF-alpha could not be detected. Alternatively, more severe hypoxia and/or phagocytosis of a significant amount of necrotic cells

(astrocytes, neural cells, tumour cells) at the site of brain damage after surgery for intra-axial tumours may active immune cells infiltrating the brain tissue (microglia, blood-derived macrophages). This could explain the additional release to TNF-alpha and IL-1ra into the CSF in this patient group, although there were no statistically significant differences in the cell numbers between the groups. The IL-10 induction may be responsible for the subsequent decrease of the pro-inflammatory cytokines in both patient groups.

However, it cannot be fully excluded that after surgery for intra-axial tumours, residual tumour cells may be producing cytokines although postoperative enhanced CT scans did not show any residual tumour. Nevertheless, decreasing cytokine levels in the later postoperative period argued against this hypothesis. Furthermore, we do not think that peri-operative dexamethasone supresses the early cytokine release into CSF, whereas the decrease of cytokine synthesis in the later postoperative period may be influenced by dexamethasone.

The activities of the measured cytokines in the brain are very wide. IL-1 and IL-6 may initiate astroglial scarring and brain repair processes [11, 23], whereas TNF-alpha and IL-8 may contribute to brain oedema [17, 30]. Furthermore it could be shown that IL-10 attenuates the astroglial reactivity and IL-1ra inhibits neurodegeneration induced by focal ischaemia or traumatic brain injury [4, 32].

Conclusions

We demonstrated that neurosurgical procedures lead to a considerable release of various cytokines into the CSF just hours after surgery. Differences in the cytokine release after surgery for intra- and extra-axial tumours seem to be the result of different stimulating conditions and different cell populations involved in cytokine synthesis. The recruitment of immune cells activated by necrotic cell components or hypoxia may lead to the release of IL-1ra and TNF-alpha. Consequently, we suppose that these cytokines may be markers for brain tissue injury. Other cytokines like IL-8 may contribute to the development of brain oedema, whereas macrophage-derived IL-10 may decrease the synthesis of pro-inflammatory cytokines after neurosurgery.

Further prospective studies in patients with traumatic brain injury might give us more detailed information about the role of immune cells and immune cell derived cytokines like TNF-alpha, IL-1ra, and IL-10 in brain destruction and repair processes. Moreover, the importance of cytokines like IL-8 for acute and delayed brain oedema after severe brain injury has to be evaluated.

Acknowledgement

This work was supported by a grant from the Charité Medical School, no. 95-028 and by a grant from the Deutsche Forschungsgemeinschaft, no. WO 621/2-1.

References

1. Aloisi F, Carè A, Borsellino G, Rosa S, Bassani A, Cabibbo A, Testa U, Levi G, Peschle C (1995) Production of hemolymphopoietic cytokines (IL-6, IL-8, colony-stimulating factors) by normal human astrocytes in response to IL-1 beta and tumor necrosis factor-alpha. J Immunol 149 (1992): 2358–2366
2. Asadullah K, Woiciechowsky C, Döcke WD, Liebenthal C, Wauer H, Volk HD, Kox W, Vogel S, von Baehr R (1995) Immunodepression following neurosurgical procedures. Crit Care Med 23: 1976–1983
3. Asadullah K, Woiciechowsky C, Döcke WD, Egerer K, Kox W, Vogel S, Sterry W, Volk HD (1996) Very low monocytic HLA-DR expression indicates high risk of infection – immunomonitoring for patients after neurosurgery and patients during high dose steroid therapy. Eur J Emerg Med 2: 184–190
4. Balasingam V, Yong VW (1996) Attenuation of astroglial reactivity by interleukin-10. J Neurosci 16: 2945–2955
5. Cassatella MA, Meda L, Gasperini S, Calzetti F, Bonora S (1994) Interleukin 10 (IL-10) upregulates IL-1 receptor antagonist production from lipopolysaccharide-stimulated human polymorphonuclear leukocytes by delaying mRNA degradation. J Exp Med 179: 1695–1699
6. Clark WC, Bressler J (1988) Transforming growth factor-beta-like activity in tumors of the central nervous system. J Neurosurg 68: 920–924
7. Daftarian PM, Kumar A, Kryworuchko M, Diaz Mitoma F (1996) IL-10 production is enhanced in human T cells by IL-12 and IL-6 and in monocytes by tumor necrosis factor-alpha. J Immunol 157: 12–20
8. Damme Jv (1994) Interleukin-8 and related chemotactic cytokines. In: Thomson A (ed) The cytokine handbook. 2nd ed. London, pp 185–208
9. Elliott LH, Brooks WH, Roszman TL (1984) Cytokinetic basis for the impaired activation of lymphocytes from patients with primary intracranial tumors. J Immunol 132: 1208–1215
10. Fontana A, Hengartner H, de Tribolet N, Weber E (1984) Glioblastoma cells release interleukin 1 and factors inhibiting interleukin 2-mediated effects. J Immunol 132: 1837–1844
11. Giulian D, Lachman LB (1985) Interleukin-1 stimulation of astroglial proliferation after brain injury. Science 228: 497–499
12. Halstensen A, Ceska M, Brandtzaeg P, Redl H, Naess A, Waage A (1993) Interleukin-8 in serum and cerebrospinal fluid from patients with meningococcal disease. J Infect Dis 167: 471–475
13. Hoch RC, Rodriguez R, Manning T, Bishop M, Mead P, Shoemaker WC, Abraham E (1993) Effects of accidental trauma on cytokine and endotoxin production [see comments]. Crit Care Med 21: 839–845
14. Karakurum M, Shreeniwas R, Chen J, Pinsky D, Yan SD,

Anderson M, Sunouchi K, Major J, Hamilton T, Kuwabara K, *et al* (1994) Hypoxic induction of interleukin-8 gene expression in human endothelium cells. J Clin Invest 93: 1564–1570
15. Kuppner MC, Hamou MF, Sawamura Y, Bodmer S, de Tribolet N (1989) Inhibition of lymphocyte function by glioblastoma-derived transforming growth factor beta 2. J Neurosurg 71: 211–217
16. Lee SC, Liu W, Dickson DW, Brosnan CF, Berman JW (1993) Cytokine production by human fetal microglia and astrocytes. Differential induction by lipopolysaccharide and IL-1 beta. J Immunol 150: 2659–2667
17. Liu T, Clark RK, McDonnell PC, Young PR, White RF, Barone FC, Feuerstein GZ (1994) Tumor necrosis factor-alpha expression in ischemic neurons. Stroke 25: 1481–1488
18. Maeda Y, Matsumoto M, Hori O, Kuwabara K, Ogawa S, Yan SD, Ohtsuki T, Kinoshita T, Kamada T, Stern DM (1994) Hypoxia/reoxygenation-mediated induction of astrocyte interleukin 6: a paracrine mechanism potentially enhancing neuron survival. J Exp Med 180: 2297–2308
19. Maimone D, Annunziata P, Simone IL, Livrea P, Guazzi GC (1993) Interleukin-6 levels in the cerebrospinal fluid and serum of patients with Guillain-Barre syndrome and chronic inflammatory demyelinating polyradiculoneuropathy. J Neuroimmunol 47: 55–61
20. Maimone D, Cioni C, Rosa S, Macchia G, Aloisi F, Annunziata P (1993) Norepinephrine and vasoactive intestinal peptide induce IL-6 secretion by astrocytes: synergism with IL-1 beta and TNF alpha. J Neuroimmunol 47: 73–81
21. Mathiesen T, Andersson B, Loftenius A, von Holst H (1993) Increased interleukin-6 levels in cerebrospinal fluid following subarachnoid hemorrhage. J Neurosurg 78: 562–567
22. McClain CJ, Cohen D, Ott L, Dinarello CA, Young B (1987) Ventricular fluid interleukin-1 activity in patients with head injury. J Lab Clin Med 110: 48–54
23. McClain C, Cohen D, Phillips R, Ott L, Young B (1991) Increased plasma and ventricular fluid interleukin-6 levels in patients with head injury [see comments]. J Lab Clin Med 118: 225–231
24. Meisel C, Vogt K, Platzer C, Randow F, Liebenthal C, Volk HD (1996) Differential regulation of monocytic tumor necrosis factor-alpha and interleukin-10 expression. Eur J Immunol 26: 1580–1586
25. Morganti Kossmann MC, Kossmann T, Brandes ME, Mergenhagen SE, Wahl SM (1992) Autocrine and paracrine regulation of astrocyte function by transforming growth factor-beta. J Neuroimmunol 39: 163–173
26. Nitta T, Hishii M, Kiyoshi S, Okumura K (1994) Selective expression of interleukin-10 gene within glioblastoma multiforme. Brain Res 649: 122–128
27. O'Nuallain EM, Puri P, Reen DJ (1993) Early induction of IL-1 receptor antagonist (IL-1Ra) in infants and children undergoing surgery. Clin Exp Immunol 93: 218–222
28. O'Nuallain EM, Puri P, Mealy K, Reen DJ (1995) Induction of interleukin-1 receptor antagonist (IL-1ra) following surgery is associated with major trauma. Clin Immunol Immunopathol 76: 96–101
29. Platzer C, Meisel C, Vogt K, Platzer M, Volk HD (1995) Up-regulation of monocytic IL-10 by tumor necrosis factor-alpha and cAMP elevating drugs. Int Immunol 7: 517–523
30. Ramilo O, Saez Llorens X, Mertsola J, Jafari H, Olsen KD, Hansen EJ, Yoshinaga M, Ohkawara S, Nariuchi H, McCracken GH (1990) Tumor necrosis factor alpha/cachectin and interleukin 1 beta initiate meningeal inflammation. J Exp Med 172: 497–507
31. Randow F, Syrbe U, Meisel C, Krausch D, Zuckermann H, Platzer C, Volk HD (1995) Mechanism of endotoxin desensitization: involvement of interleukin 10 and transforming growth factor beta. J Exp Med 181: 1887–1892
32. Relton JK, Rothwell NJ (1992) Interleukin-1 receptor antagonist inhibits ischaemic and excitotoxic neuronal damage in the rat. Brain Res Bull 29: 243–246
33. Renno T, Lin JY, Piccirillo C, Antel J, Owens T (1994) Cytokine production by cells in cerebrospinal fluid during experimental allergic encephalomyelitis in SJL/J mice. J Neuroimmunol 49: 1–7
34. Roszman TL, Brooks WH, Elliott LH (1987) Inhibition of lymphocyte responsiveness by a glial tumor cell-derived suppressive factor. J Neurosurg 67: 874–879
35. Sharief MK, Thompson EJ (1992) In vivo relationship of tumor necrosis factor-alpha to blood-brain barrier damage in patients with active multiple sclerosis. J Neuroimmunol 38: 27–33
36. Tada M, de Tribolet N (1993) Recent advances in immunobiology of brain tumors. J Neurooncol 17: 261–271
37. Tada M, Sawamura Y, Sakuma S, Suzuki K, Ohta H, Aida T, Abe H (1993) Cellular and cytokine responses of the human central nervous system to intracranial administration of tumor necrosis factor alpha for the treatment of malignant gliomas. Cancer Immunol Immunother 36: 251–259
38. Tada M, Diserens AC, Desbaillets I, Jaufeerally R, Hamou MF, de Tribolet N (1994) Production of interleukin-1 receptor antagonist by human glioblastoma cells in vitro and in vivo. J Neuroimmunol 50: 187–194
39. Tracey KJ (1996) Tumour necrosis factor-alpha. In: Thomson A (ed) The cytokine handbook. 2nd ed. London, pp 289–304
40. Van Meir EG (1995) Cytokines and tumors of the central nervous system. Glia 15: 264–288
41. Wanidworanum C, Strober W (1993) Predominant role of tumor necrosis factor-alpha in human monocyte IL-10 synthesis. J Immunol 151: 6853–6861
42. Woiciechowsky C, Asadullah K, Schöning B, Nestler D, Vogel S, Döcke WD, Volk HD (1996) Neurosurgery induces only local signs of inflammation but systemic antiinflammation and immunodepression: role of neuroendocrine stress response. [Abstract] Immunobiology 196: 86
43. Yamauchi Takihara K, Ihara Y, Ogata A, Yoshizaki K, Azuma J, Kishimoto T (1995) Hypoxic stress induces cardiac myocyte-derived interleukin-6. Circulation 91: 1520–1524

Comment

This paper measures the levels of several inflammatory cytokines before, during and after operation for intracranial and intracerebral tumours. It is descriptive and it is hard to assess the significance of the data. However, it seems novel and potentially interesting; the data could be compared to those seen after severe brain injury, explaining the role of cytokines in the mechanism of secondary brain damage.

Correspondence: Christian Woiciechowsky, M.D., Universitätsklinik für Neurochirurgie, Virchow-Klinikum, Medizinische Fakultät der Humboldt-Universität zu Berlin, Augustenburger Platz 1, D-13353 Berlin, Federal Republic of Germany.