

INTERLEUKIN-6 AND GRANULOCYTE MACROPHAGE-CSF IN THE CEREBROSPINAL FLUID FROM HIV INFECTED SUBJECTS WITH INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM

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SUMMARY — We detected the cytokines interleukin-6 (IL-6) and granulocyte macrophage-CSF (GM-CSF) by ELISA in the CSF and serum of 30 HIV-infected patients classified as AIDS dementia complex (ADC), and 20 subjects with other neurological diseases (OND). We have found a high incidence of detectable IL-6 and GM-CSF in the CSF of ADC patients compared with OND patients. No statistical differences were observed between both groups for serum IL-6 and GM-CSF levels. These results suggest an intrathecal synthesis of these cytokines and a possible involvement in the pathogenesis of ADC.

KEY WORDS: AIDS dementia complex, cerebrospinal fluid, cytokines (interleukin-6, granulocyte-macrophage-CSF).

Interleucina-6 e granulócito-macróforo-CSF no líquido cefalorraquidiano de pacientes infectados por HIV com comprometimento do sistema nervoso central.

RESUMO — Detectamos as citocinas interleucina-6 (IL-6) e granulócito-macróforo-CSF (GM-CSF) por ELISA no LCR e soro de 30 pacientes infectados por HIV classificados como tendo AIDS-demência complexo (ADC) e de 20 pacientes com outras doenças neurológicas (OND). Encontramos elevada incidência de IL-6 e GM-CSF detectável no LCR de pacientes com ADC, em relação aos pacientes com OND. Diferenças estatísticas não foram observadas entre os dois grupos de pacientes para níveis de IL-6 e GM-CSF no soro. Esses resultados sugerem síntese intratecal dessas citocinas e sua possível participação na patogenia da ADC.

PALAVRAS-CHAVE: AIDS-demência complexo, líquido cefalorraquidiano, citocinas (interleucina-6, granulócito-macróforo-CSF).

Interleukin-6 (IL-6) and granulocyte-macrophage CSF (GM-CSF) are polypeptide substances produced by monocytes/macrophages and other cell types. IL-6 is a cytokine that promotes differentiation of B-cells to antibody-secreting cells. IL-6 works synergistically with IL-1 to promote B-cell growth, and it has a wide variety of biological activities including mediation of fever and the acute phase response of inflammation⁵. The GM-CSF stimulate the production of both granulocytes and macrophages in cultures of human and murine bone marrow cells. Little is known of the pattern of IL-6 and GM-CSF production in human nervous diseases⁴. Several studies have suggested a possible role in the pathogenesis of AIDS dementia complex (ADC), but the mechanism of this disease is unclear.

In the present study we assayed the IL-6 and GM-CSF in paired cerebrospinal fluid (CSF) and serum from ADC patients, using a sensitive, specific and non-cross reactive ELISA.

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MATERIALS AND METHODS

We studied 30 patients (23 men; 7 women) with a mean age of 32 years affected by definite ADC, according to the criteria of the Center for Disease Control¹. We also studied 20 subjects with a mean age of 36 years with one of the following other neurological diseases (OND): headache, meningioma, degenerative disk problems, metabolic polyneuropathy, hereditary degenerative ataxia. Serum and CSF samples were obtained simultaneously from all subjects; all CSF samples had normal levels of protein, glucose and cells; xanthochromic specimens and those with more than 1 red blood cell per field were excluded.

Serum and CSF levels of IL-6 and GM-CSF were simultaneously detected by 2 ELISA kits (Genzyme Co, Boston, USA), according to manufacturer instructions. Both serum and CSF were diluted 1:1. The sensitivity of each ELISA is as follows: GM-CSF 7.5 pg/ml; IL-6 20 pg/ml. The levels of IL-6 and GM-CSF in serum and CSF were measured in duplicate and the results were expressed as the mean \pm SD. Statistical analysis was performed using Student t test and Spearman's rank correlation test.

RESULTS

The IL-6 level in the CSF of patients with ADC was significantly higher than in the OND patients ($p < 0.05$). Also the CSF GM-CSF concentration was significantly increased in respect to control group ($p < 0.05$). No statistical difference was observed in serum IL-6 and GM-CSF levels among ADC patients and control group (Table 1).

No significant correlation between serum and CSF concentrations of GM-CSF and IL-6 was observed.

Table 1. Interleukin-6 (IL-6) and granulocyte macrophage-CSF (GM-CSF) in serum and CSF of patients with AIDS dementia complex (ADC) and other neurological diseases (OND) ($m \pm SD$).

| | ADC | | OND | |
|--------|------------------|-----------------|----------------|----------------|
| | CSF | Serum | CSF | Serum |
| IL-6 | 94.2 \pm 32.3* | 20.5 \pm 10.6 | 20.6 \pm 9.8 | 21.1 \pm 7.8 |
| GM-CSF | 42.4 \pm 18.0* | 7.5 \pm 3.5 | 4.2 \pm 7.1 | 6.4 \pm 8.1 |

* $p < 0.05$, respect to OND patients.

COMMENTS

Neurological disease is recognised as a common manifestation of HIV infection. Around 10 per cent of AIDS patients present initially with neurological symptoms and as many as 70% of all patients with AIDS may develop clinical involvement of the nervous system at various stages. HIV has been isolated from CSF and found in all parts of the nervous system. However, signs and symptoms of neurological complications in HIV infected individuals may be due to particularly indirect effects of HIV itself.

The ADC, sometimes called subacute encephalitis, is one of the most important neurological complications. In the ADC the neurones may be infected directly by HIV, but the evidence for a truly direct infection of these cells is equivocal⁶. However, monocytes and macrophages are known to become HIV infected and may act as the source of infection for other types of brain cells⁶. Probably of greater importance is the production of cytokines, monocyte-derived, released from infected cells which may cause tissue damage.

The present study shows an increase of IL-6 and GM-CSF only in the CSF of ADC patients. These data suggest an intrathecal synthesis from macrophages, which may cause brain damage in ADC patients. By contrast most ADC patients did not have detectable IL-6 and GM-CSF serum levels. The failure to detect serum IL-6 and GM-CSF is in agreement with other reports^{2,3}.

In conclusion, we think that the macrophages are important in the ADC pathogenesis, but further studies are needed to clarify the relationship between CSF cytokine accumulations and aspects of clinical course in ADC.

Acknowledgements — The authors wish to thank the precious assistance and courtesy of Prof. Sergio Novis and Dr. Marzia Puccioni from the Department of Neurology, Federal University of Rio de Janeiro. This research was supported in part by grants from Ist. Sup. Sanità, Italy (Research contract 6203-004, AIDS Project).

REFERENCES

1. Center for Disease Control. Classification system for human T-lymphotropic virus type III/lymphadenopathy-associated virus infection. *MMWR* 1986, 35:334-339.
2. Frei K, Malipiero UV, Leist TP, Zinkermagel RM, Seliwab ME, Fontana A. On the cellular source and function of interleukin-6 produced in the nervous system in viral diseases. *Eur J Immunol* 1989, 19:689-694.
3. Gallo P, De Rossi A, Amadori A, Tavolato B, Chieco-Bianchi S. Central nervous system involvement in HIV-infection.' *AIDS Res Hum Retrovirus* 1988, 4:211-221.
4. Hauser SL, Doolittle TH, Lincoln BS, Brow RH, Dninarelo CA. Cytokine accumulations in CSF of multiple sclerosis patients: frequent detection of interleukin-1 and tumor necrosis factor but not interleukin-6. *Neurology* 1990, 40:1735-1739.
5. Muraguchi A, Hirano T, Rang B, et al. The essential role of B cell stimulatory factor (BSF-2/IL-6) for the terminal differentiation of B cells.' *J Exp Med* 1988, 86:6348-6352.
6. Weiler IVD. The management of neurological aspects of HIV infections. In Kennedy PG (ed): *Epidemiology and Disease Spectrum*. UK: Colwood House Med Publ 1989, p 7-11.