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Cerebrospinal Fluid Cytokine and Chemokine Patterns in Central Nervous System Infections, Hemorrhage and Neoplasms

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ABSTRACT

Cytokines and chemokines are soluble proteins that act as regulators of cellular functions throughout the body. Cytokines and chemokines released in the setting of various CNS disorders appear in the CSF compartment where determination of their levels can provide insight into pathogenic processes such as neuroinflammation. We utilized the Millipore HCYTOMAG 60K assay/kit/system to perform multiplex profiling of 42 different cytokines/chemokines in the CSF of patients with a variety of distinct CNS disease processes, including infection, hemorrhage and neoplasia. CNS infections included viral (Chronic Parechovirus type 3 (HPeV3), Enterovirus (EV) 68, Adenovirus, JC virus, West Nile virus), bacterial (*Mycobacterium tuberculosis, Borrelia burgdorferi, Propionibacterium acnes, Staphylococcus epidermidis, Streptococcus sp.*), fungal (*Cryptococcus neoformans*) and single celled parasite (*Toxoplasma gondii*). CSF specimens negative for infectious organisms in non-inflammatory conditions were selected as controls. Additional non-infectious samples tested were obtained from patients with subarachnoid hemorrhage (SAH) and following surgery for glioblastoma. The glioblastoma samples were noteworthy in having negligible elevations in the cytokines/chemokines tested. CSF from patients with SAH was elevated in only MCP-1/CCL2. Distinct patterns of cytokine/chemokine expression were detected for each infectious patient population. Picornavirus infections HPeV3 and EV68 were associated with increased levels of the monocyte chemoattractant protein MCP-1/CCL2 when compared to non-infectious, non-inflammatory samples. In contrast to chronic HPeV3 infection, EV68 encephalitis was associated with increased CSF levels of additional cytokines; CCLX1, IL-4 and IL-7. Adenovirus infection was associated with markedly higher levels of fractalkine in CSF when compared to any of the other non-inflammatory, infectious, hemorrhage or tumor cases. CSF from a *Mycobacterium tuberculosis* infection demonstrated increased levels of a greater variety of cytokines/chemokines than any of the other groups tested. Patterns of cytokine/chemokine expression in the CNS reveal characteristics of the host innate response that provide insight into the disease process and potential targets for therapeutic intervention.

INTRODUCTION

Because of its relationship to the critical structures of the central nervous system (CNS), the cerebrospinal fluid (CSF) compartment reflects the current state of the CNS, especially in neurological diseases. When pathogens invade the CNS, the inflammatory cascade hinges upon the expression of pro and anti-inflammatory chemokines and cytokines, which become detectable in the CSF. Because various bacterial and viral pathogens utilize various mechanisms to elicit host response, the patterns of chemokine and cytokines released during these various infections are different. A variety of cells including monocytes/microglial cells play a role in initiating, coordinating, and regulating the innate response to infectious agents and other stimuli via expression of a variety of chemokines/cytokines.

Routine laboratory testing of the CSF (cell counts, microbiology, etc.) are essential in the initial evaluation of certain disease processes; however, they are affected by various factors such as disease time course, organism burden, and test parameters. For instance, in up to 30% of cases of suspected viral meningitis/encephalitis, no definite virus is identified. By studying the cytokine/chemokine profiles of various infections, these patterns may be able to provide insight into the type of infectious agent involved in such cases. Additionally, since many CNS infections are not histologically analyzed during active infections, chemokine/cytokine profiles may be the most immediate parameter available to gain insight into how a particular, pathogenic agent acts on the brain. **CSF cytokine/chemokine analysis provides an incredible wealth of information which may help narrow differential diagnosis, understand disease pathophysiology, and—with further studies—help predict clinical course and disease outcome.**

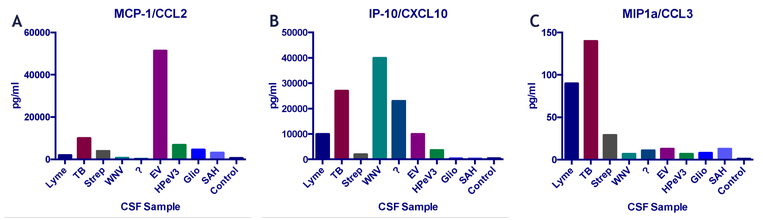
METHODS

We utilized the Millipore HCYTOMAG 60K assay/kit/system to perform multiplex Elisa profiling of 42 different cytokines in the CSF of patients with a variety of CNS disease processes along with control (non-infectious, non-tumor, non-hemorrhagic) samples. We focused on the clinical cases with one, single disease process present. The cases reported include Lyme neuroborreliosis (Lyme) in a 48 year old man, fatal mycobacterium tuberculosis meningitis (TB) in an immunosuppressed woman on adalimumab therapy, *Streptococcus mitis* meningitis (Strep) in a 73 year old man following repair of a lumbar pseudomeningocele, West Nile Virus encephalitis (WNV) in 33 year old man, clinically suspected viral encephalitis (?) in 20 year old woman, enterovirus encephalitis (EV) in 19 year old male, chronic human parechovirus type 3 encephalitis (HPeV3) in an 18 year old woman, two cases of glioblastoma (GBM), subarachnoid hemorrhage (SAH) secondary to rupture of cerebral saccular aneurysm and three controls that were negative for infectious organisms and had normal CSF findings. The following cytokines reported in the table since demonstrated at least a five fold increase compared to controls in one of the disease processes selected for review.

RESULTS Chemokine/cytokine levels (pg/ml) in a variety of disease processes are presented in the table.

- There is a general elevation of **MCP-1/CCL2** levels in the cases.
- **IP-10/CXCL10** levels are higher in infectious cases.
- **MDC/CCL22** and **MIP1a/CCL3** levels are more elevated in bacterial compared to viral Infections.
- VEGF The highest levels of **VEGF** are present in the CSF from patients with glioblastomas.
- **MDC/CCL22** levels from both picornavirus encephalitis (EV and HPeV3) cases are lower or similar to control levels in CSF.
- Several chemokines/cytokines from the **HPeV3** case show no increase or less than a five fold increase in levels compared to control values.
- **GRO/CXCL1, IL-6 and IL-8** levels are elevated in **bacterial infections**, the **WNV case**, and **EV case**.
- **MCP3/CCL7** levels are markedly elevated in **TB**.
- Elevated **IL-17** levels present in **Lyme** and **Strep** may suggest a component of TH-17 immune response in these infections.

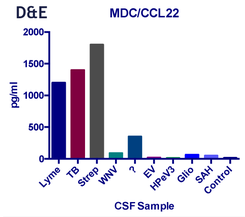
Chemokine /Cytokine	Lyme	TB	Strep	WNV	?	EV	HPeV3	GBM	SAH	Control ± Standard error
MCP-1	2,000	10,000	4,000	790	334	51,409	6,830	4,600	3,207	683 ±94
IP-10	10,000	27,000	2,000	40,000	23,075	10,000	3,674	416	384	447 ±82
MDC	1,200	1,400	1,800	90	352	20	13	65	51	15 ±2.7
MIP1a	90	140	29	7	11	13	7	8	13	1 ±0.17
IL-6	17	6,800	41,225	320	3	2,362	3	438	66	3 ±0.62
IL-8	600	2,600	3,700	260	45	20,000	108	5,100	157	36 ±11
GRO	220	600	10,000	110	35	10,000	15	2,800	83	19 ±2.0
G-CSF	40	1276	130	270	13	750	22	60	16	10 ±1.9
sCD40L	102	89	100	16	160	28	27	25	14	7 ±1.8
IL-1Ra	81	200	41	16	3	70	8	12	7	3 ±0.68
VEGF	24	162	68	11	18	26	9	2400	12	4 ±1.4
FGF-2	35	65	57	3	8	24	10	30	17	3 ±0
IL-10	147	261	55	8	10	18	3	21	4	2 ±0.21
RANTES	58	300	9	7	70	9	3	4	3	2 ±0.22
IL-17	6	4	6	2	4	2	1	2	1	1 ±0.04
IL-5	3	2	41	2	2	2	2	2	2	2 ±0.05
MCP3	15	1,700	24	8	7	69	8	12	8	6 ±0.28



*A. **MCP-1 /CCL2** is an indicator of a **pro-inflammatory response**.*

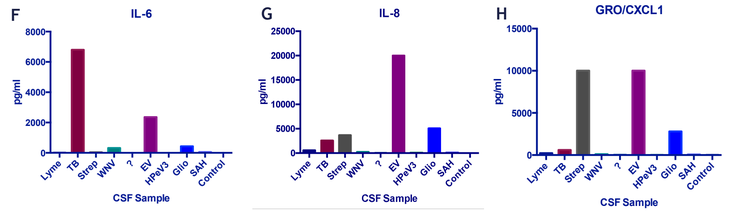
*B. **IP-10/CXCL10** elevation suggests an **infectious** process.*

*C. **MIP1a/CCL3** may serve as a marker for **active pathogen replication**.*



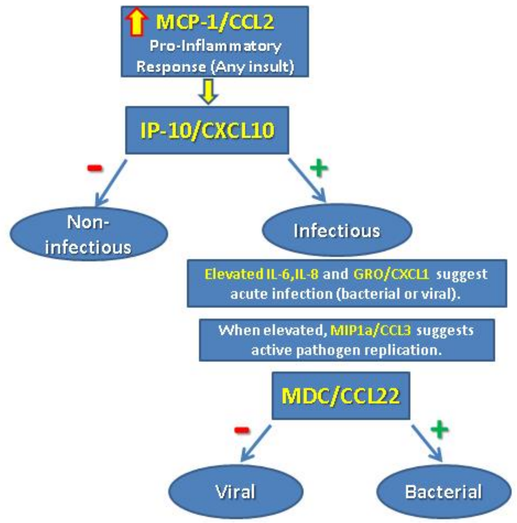
*D. **MDC/CCL22** elevation suggests a **bacterial infection** rather than a viral process.*

*E. **Very low levels of MDC/CCL22** seen in **picornavirus** encephalitis (EV and HPeV3) may represent a distinct pro-inflammatory response.*



*F-H. **IL-6, IL-8, and GRO/CXCL1** levels appear to be elevated in acute infections and may be an indicator **infection activity**.*

Can Cytokine/chemokine profiles provide information about a pro-inflammatory case of unknown etiology?



USING CSF CYTOKINE/CHEMOKINE PROFILES IN CLINICAL PRACTICE CASE STUDY: ?

20 year old woman presented with headache, photophobia, neck stiffness for the past few days. She reported recent sick contacts. Lumbar puncture performed showed CSF lymphocytosis, elevated opening pressure, and elevated protein. All CSF microbiology studies were negative.

INTERPRETATION:
-Elevated **MCP-1** and **IP-10** support pro-inflammatory process, a probable infectious type.
-Low **MIP1a** may reflect decreased pathogen replication.
-**MDC** values suggest viral etiology.
-Low **IL-6, IL8** and **GRO** suggest possibly resolving infection.

The clinicians suspected a viral meningitis. The patient was discharged the next day secondary to clinical improvement.

CONCLUSIONS

1) **Cytokine/chemokine profiles are different in various CNS disease processes.**
2) **Cytokine/chemokine profiles may be useful in determining the nature of the inflammatory process, especially in the setting of inconclusive microbiology tests.**
3) **In the context of a pro-inflammatory state, very low levels of MDC/CCL22 may represent a distinct pro-inflammatory response , possibly related to deficient anti-inflammatory mechanisms.**
4) **With further studies, CSF cytokine/chemokine profiles will provide more information, including predictions regarding clinical course and disease outcome.**