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The Cerebrospinal Fluid Presentations of Neuro-Behçet Disease, A Way to Know the Ethiopathogenesis and Improve Armamentarium

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ABSTRACT

Neuro-Behcet's disease (NBD) is a rare but potentially fatal manifestation of Behcet's disease. Common presentations of neuro-Behcet's disease are parenchymal (brainstem and hemispheric manifestations, meningoencephalitis, spinal cord lesions) and non-parenchymal (arterial occlusions, aneurysms, Dural sinus thrombosis). Cerebrospinal fluid (CSF) findings in parenchymal NBD usually show an inflammatory pattern with elevated cell count (usually high levels of polymorphonuclear leukocytes), high protein, and normal glucose levels, whereas the CSF findings in non-parenchymal NBD could be normal except for high opening pressure. Further investigation of CSF in parenchymal NBD has demonstrated elevated Natural killer T cells, high inflammatory chemokines, and cytokines such as Tumor Necrosis Factor-alpha (TNF- α), Interferon-gamma (IFN-γ), Interleukin (IL)12, IL-6, IL-17, IL-26, IL-15, Vascular endothelial growth factor (VEGF), Matrix metallopeptidase 9 (MMP-9), chemokine [C-X-C motif] ligand 8 (CXC-8) which indicate the role of both innate and adaptive immunity in this disease. Particularly, T helper type 1 (TH-1) and TH-17 pathways are implicated in the pathogenesis of this condition. Successful use of certain biologic agents such as TNF and IL-6 inhibitors in NBD further emphasizes the role of inflammatory cytokines in the immunopathogenesis of the disease. Drugs blocking the TH 17 pathway such as ustekinumab, secukinumab could also be applicable in the process. This review summarizes the detailed CSF findings in NBD, current understanding of the immunopathogenesis of NBD, and treatment of NBD with specific biologic agents based on our understanding of the disease pathogenesis.

Keywords: Behcet's Syndrome, Cerebrospinal Fluid, Neuro-Behcet's Syndrome, Pathogenesis, Pathology

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INTRODUCTION

Neurologic manifestations of Behcet's disease (BD), Neuro-Behcet's disease (NBD), is a rare but grave presentation of BD (1). Central nervous system presentations of NBD can be classified into two groups: 1) parenchymal involvement including brainstem involvement, hemispheral, and spinal manifestations, and meningoencephalitic presentations; and 2) non-parenchymal involvement including venous thrombosis and arterial involvement (2).The exact etiopathogenesis of NBD remains to be elucidated. Pathogenesis of parenchymal NBD and nonparenchymal NBD might be different (3). In this review, we have described detailed Cerebrospinal fluid (CSF) findings in NBD along with plausible immunopathogenesis of this rare condition.

Cerebrospinal Fluid Findings in Neuro-Behcets Disease

Cerebrospinal fluid (CSF) findings in NBD are dependent on NBD pathogenesis and pathology. Vasculitis and less commonly vasculopathy are the pathologic presentation of NBD. In biopsy specimens from patients with NBD, infiltration of polymorpho- or mono-nuclear and rarely eosinophilic might be seen around the vessels (3). In parenchymal NBD, CSF opening pressure is often within normal limits. CSF cell count is usually less than 200/mm3. Pleocytosis is lymphocyte or less frequently polymorphonuclear leukocytes (PMN)- dominant. Occasionally, CSF cell count may be normal in this condition. CSF protein is usually higher than normal, but it might be normal too. CSF glucose is often normal, which can be an aid in the differentiation of acute NBD from infectious meningitis. In parenchymal NBD, particularly in chronic progressive patients, Interleukin (IL) -6 is usually increased and might represent disease activity. In NBD associated with cerebral venous sinus thrombosis, opening pressure is elevated, but CSF parameters are usually unremarkable (4). Oligoclonal Immunoglobulin G (IgG) bands are infrequently found in a minority of NBD patients. The CSF findings in NBD and its mimics were summarized in Box-1 and Table 1.

Among the specific cell types demonstrated in the CSF of patients with NBD, Natural Killer T cells (NKT cells), were found to be elevated in the CSF during active disease and subsequently reduced during remission (18, 19)

Various studies have shown high levels of inflammatory cytokines and chemokines in the CSF in NBD such as chemokine [C-X-C motif] ligand 8 (CXC-8) or IL-8, a neutrophil chemoattractant, Vascular endothelial growth factor (VEGF), an inflammatory chemokine which recruits inflammatory cells such as lymphocytes and monocytes (20), Matrix metallopeptidase 9 (MMP-9), secreted by PMN leukocytes and β2-microglobulin expressed from CSF lymphocytes (21). However, elevated chemokines are not specific for NBD and have been observed

Box 1. CSF Findings in Neuro-Behcet's Disease

Parenchymal NBD:
Opening pressure: Normal in parenchymal NBD
Cell: Increased, usually less than 200/$mm^{3,}$ Usually lymphocyte-dominant
Protein: Usually increased
Glucose: Usually normal
OCB: positive in 15-20% of patients
IL-6: Increased, might represent disease activity
NBD with CVST:
Opening pressure: elevated
Cell: Usually Normal
Protein: Usually normal
Glucose: Usually normal

Table 1. Characteristics of CSF components in NBD and major differential diagnoses (1, 4, 5-17)

	Cell cells/mm3	Lymphocyte/ PMN predominance	Protein (mg/dl)	Glucose (mg/dl)	OCB Positivity	IL-6
Normal*	0-3	Lymphocyte dominant	<45	>40	-	-
NBD	50<<200	Lymphocyte or PMN dominant	Mildly increased	Often Normal	15-20%	Increased, might represent disease activity
MS	<50	Mostly lymphocyte dominant	Mildly increased	Almost always Normal	35–68 (first event); 90 (established MS)	Increased, Might correlate with clinical and radiologic disease activity
Chronic infectious Meningitides	50<<500	Mostly lymphocyte dominant Rarely PMN	Increased	Often decreased	95%in neuro-syphilis and 80% in neuro-borreliosis	Increased Sparse data
CNS-Vasculitides	<50	Mostly lymphocyte dominant	Increased	Often Normal	25-60%	Increased
Carcinomatous meningitis	5<<500	Mostly lymphocyte dominant	Increased	Normal or decreased	30%	Increased Sparse data

*In adult population

in other inflammatory conditions such as multiple sclerosis (22-24).

High levels of Tumor necrosis factor- alfa (TNF- α), a potent stimulator of MMP-9, Interferon-gamma (IFN-γ), IL-12, which stimulates the T helper type 1 pathway, have been observed in the CSF of NBD patients (24-26) High CSF levels of IFN-γ, cytokines downstream to IFN-γ such as C-X-C motif chemokine 10 [CXCL10] or Interferon gamma-induced protein 10, have been reported in NBD (24). IL-15 and VEGF, found elevated in CSF of NBD, stimulates proliferation of NK cells and induces production of IFN-γ and TNF-α (5).

Various groups previously showed high IL-6 and IL-6-m-RNA in the CSF in NBD (14-20)

High CSF levels of IL-17 , IL-17A , and IL-26, a TH17 effector cytokine, in active NBD compared to control and non-inflammatory neurological diseases have been noted (27-33) On the other hand, IL-37, an anti-inflammatory cytokine and inhibitor of the TH 17 pathway, was found to be low in the CSF of NBD patients and subsequently increased after treatment when the disease is in remission (34-36).

CSF from NBD patients was found to have higher levels of IL-33 and IL-33 messenger ribonucleic acid (mRNA), a member of the IL-1 superfamily which acts as an "alarmin", in comparison to the controls (37).

High CSF levels of B cell-activating factor of the tumor necrosis factor family (BAFF) and BAFF-R (BAFF receptor) noted in NBD (38, 39).

Among the transcription factors, in NBD subjects increased CSF expression of T-Box Transcription Factor 1 (TBX1), RAR Related Orphan Receptor C (RORC) and forkhead box P3 (FoxP3) were noted. The ratio of increase in the RORC/FOXP3 and TBX21/ GATA Transcription factors were high in NBD patients indicating activation of both TH1 and TH17 pathways (40).

GATA transcription factors are a family of transcription factors which can bind to the DNA sequence "GATA". Higher expression of retinoid acid or androgen receptor AR-related orphan receptor gamma (RORγt) gene expression was observed compare AR-related orphan receptor gamma d to non-inflammatory neurological diseases (24).

Some studies have also reported high CSF levels of FoxP3, the transcription factor for Regulatory T cells (Treg) pathways, and high IL-10 levels, a Treg cytokine, in parenchymal NBD compared to multiple sclerosis and control subjects (26, 41).

Implications of CSF Findings in the Immunopathogenesis of NBD

There is limited data on the pathogenesis of NBD. Few studies on the CSF analysis in this condition give a clue to the immunopathogenic pathway. Based on high CSF levels of various cytokines and chemokines, both innate and adaptive immunity have been implicated in the pathogenesis of NBD (Figure 1) (42). Natural Killer T cells (NKT cells), found in high levels in the CSF of patients with Inflammatory bowel disease (IBD), belong to the innate immune system (43).

In vitro expansion of these NKT cells revealed the presence of mostly matured NKT cells releasing IFN-γ which helps in the differentiation of T helper cells into TH1 phenotype and thereby acts as a bridge between innate and adaptive immune response in NBD (43).

The presence of high CSF levels of neutrophil chemoattractants such as MMP9, CXC8 also indicates the involvement of innate immunity.

In Tasci et al.'s study, CSF anti-Heat shock proteins 65 (anti-hsp65) antibodies were positive in about half of the patients with parenchymal NBD (44). Heat shock proteins (HSP) proteins are proinflammatory and stimulate both innate and adaptive immune response. In peripheral blood mononuclear cells (PBMCs), HSP stimulation leads to the release of proinflammatory cytokines including IFN-γ, IL-12, TNF-α and lowers the levels of IL-4 and IL-10, thus favoring a TH1 response (45).

T helper cells have a critical role in the pathogenesis of NBD. Inflammation in NBD is mediated by TH1 and TH17 pathways. Differentiation of the T Helper cells into different subsets is regulated by specific transcription factors. T-Box Transcription Factor 21 (TBX21) and retinoid-related orphan nuclear receptor C (RORC) mRNA transcript variant 2 are required for TH1

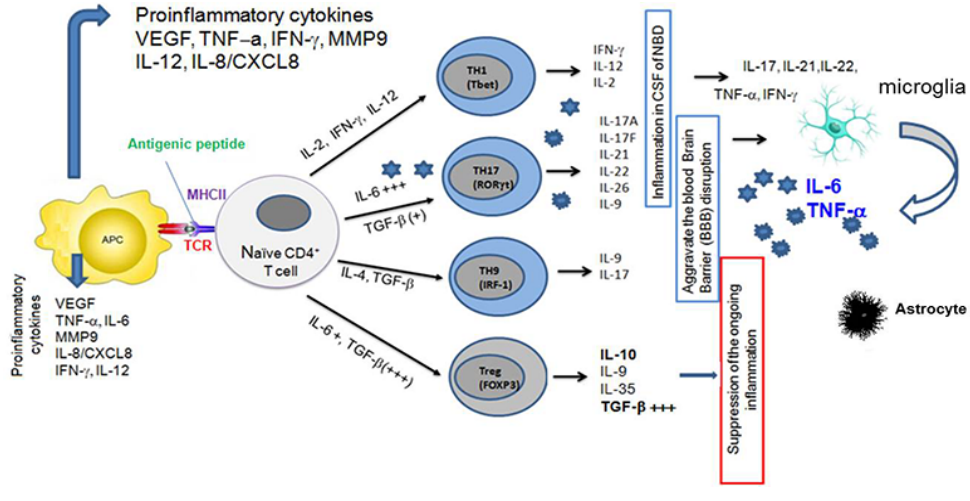

Figure 1: The role shows the role of the T cells and different cytokines in the pathogenesis of Neuro Behcet's Disease. TH1 and TH17 cells play a major role in the pathogenesis, whereas anti-inflammatory cytokines released by the Treg cells have a protective effect. APC: Antigen Presenting cells; VEGF: Vascular Endothelial Growth Factor; MMP: Matrix Metalloproteinase; IL: Interleukin; IFN: Interferon; TCR: T Cell Receptor

and TH 17 differentiation respectively. Transcription factor FOXP3, on the other hand, leads to differentiation into Treg type and GATA3 is the transcription factor for Th2 differentiation. In NBD subjects increased CSF expression of TBX21, RORC and FoxP3 were shown by Hamzauoui et al. The ratio of increase in the RORC/FOXP3 aTHnd TBX21/ GATA3 Transcription factors were high in NBD patients indicating activation of both TH1 and TH17 pathway (40).

IFN-γ, which is found to be elevated in the peripheral blood PBMCs and CSF of patients with NBD, is essential for the differentiation and proliferation of TH1 cells. Differentiated TH1 cells further release IFN-γ and self perpetuates the cycle (26). IL-12 is the other major cytokine responsible for TH1 differentiation and has been found in high concentrations in the CSF in subjects with NBD (24). High CSF levels of cytokines downstream to IFN-γ such as CXCL10 or Interferon gamma-induced protein 10, further demonstrates the role of the TH1 pathway (24).

An interesting observation in the CSF of NBD subjects was high levels of B cell-activating factor of the B-cell-activating factor (BAFF) and BAFF-R [BAFF receptor] (46). In Sumita et al.'s study, BAFF, secreted in the central nervous system, was implicated in the pathogenesis of progressive NBD (39). T cell function can be modulated by BAFF. Stimulated T cells produce more IFN-γ in presence of BAFF leading to activation of TH1 pathway (38).

Over the last few years, multiple studies have established the role of the TH17 pathway in BD and NBD (28, 30).Various groups previously showed high IL-6 and IL-6-mRNA in the CSF in NBD as mentioned earlier (27, 29, 33).

IL-6 is one of the major inducers of the TH17 pathway (31, 32) High CSF IL-6 level in NBD can help to differentiate the disease from other inflammatory neurological conditions like Multiple sclerosis (MS), Subacute sclerosing panencephalitis (SSPE). Among the different types of NBD, chronic progressive neuro-BD subtype has the most pronounced increase in IL-6 levels (47). In parenchymal NBD, IL-6 level was demonstrated to be discriminatory between active disease/ flare vs disease in remission. During the flare, CSF IL-6 level increases simultaneously with CSF protein and cell counts. However, in chronic progressive NBD, although the CSF IL-6 level is usually high, cell count and protein level in CSF may be normal. Under these circumstances, CSF IL-6 level may be helpful levels for diagnostic and monitoring purposes. The absolute value of CSF IL-6 of 20 pg/ ml has been reported to be associated with poor outcome in NBD (48). β2 microglobulin, an inducer of IL-6, was found to be elevated in the CSF in a small cohort of NBD patients (21).

Another group recently showed high CSF levels of IL-17 in active NBD compared to control (49).

At the transcription level, CSF studies in NBD demonstrated higher expression of RORγt gene expression compared to non-inflammatory neurological diseases. The same study also demonstrated a significantly higher expression of IL-17a in CSF samples from NBD in comparison with non-inflammatory neurological diseases (24).

Interleukin-26, a TH-17 effector cytokine, demonstrated at a high level in CSF from patients with BD, positively correlated with IL-17 level. IL-26-stimulated CD 4+ T cells and monocytes stimulate secretion of TH17 (IL-17A, IL-23) and inhibit Treg (IL-10, TGF-β) cytokines. IL-26 further leads to the expression of pro-inflammatory cytokines in BD, such as IL-1β, IL-6, and TNF alfa by stimulation of the monocytes (18). CSF IL-26 levels have a negative correlation with the level of IL-37 (50). IL-37 is an anti-inflammatory cytokine that inhibits activation of the TH-17 pathway. Dendritic cells acquire immune tolerance in presence of IL-37 and consequently adaptive immune response is diminished (36). Dhifallah et al. demonstrated low CSF levels of IL-37 in NBD and subsequent increase in the level of

the same after treatment when the disease is in remission. CSF level of IL-37 negatively correlates with inflammatory cytokines IL-6, IL-17, and IL-21 levels (34).

Traditionally TH2 pathway was postulated to be suppressed in BD (51). In Hamzoui et al.'s study, CSF from NBD patients was found to have higher IL-33 levels in comparison to the controls. IL-33 mRNA was also highly expressed. Nuclear factor kB (NF-kB), which facilitates IL-33 transcription, was increased in comparison to disease controls as well (52). IL-33 belongs to the category of the IL-1 superfamily. It is secreted in necrotic or damaged cells, and acts as an "alarmin". It activates the innate immune system, as well as T helper 2 (Th2) immune responses (37). Few studies have reported activation of Treg cells in NBD as evidenced by high CSF level of FoxP3, the transcription factor for the Treg pathway. CSF samples from NBD have shown high IL-10 levels, a Treg cytokine, in parenchymal NBD compared to multiple sclerosis and control subjects (41). It has been postulated that the anti-inflammatory effect of IL-10 may downregulate the inflammatory cytokine IFN gamma and have a protective effect in BD (26).

Bahrini et al study demonstrated higher CSF levels of CD39 but not CD73 in patients with NBD. CD39 was preferentially expressed on B cells of NBD (27).

CD-39 and CD-73 are exonucleases that covert ATP/ADP to AMP and ATP-induced pro-inflammatory reactions. Alteration in Cluster of Differentiation (CD)39 and CD-73 has been described in multiple autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease (53). An illustration of immune-pathogenesis of NBD was presented in Figure 1.

Therapeutic Implications

The mainstay of treatment of NBD is corticosteroids and conventional immunomodulatory drugs. Over the last decade, monoclonal antibodies against specific cytokines or cytokine receptors, implicated in the immunopathogenesis of NBD, are being increasingly used with promising results. Anti-tumor necrotic factor-alpha (anti-TNFα) drugs such as infliximab, adalimumab, etanercept have been used for the treatment of NBD for the longest period among all the biologic medications with significant improvement in symptoms in various case series. (29, 54-56)

Considering the increased levels of IL-6 in the CSF of some patients with NBD, Tocilizumab was advocated for treatment of NBD (57). The first case report of successful use of tocilizumab in NBD with brainstem involvement was reported by Shapiro et al. After failing to respond to infliximab and daclizumab, rapid clinical improvement was observed within a few days and in seven months complete remission was achieved with tocilizumab (58). Some other case reports also demonstrated significant improvement of NBD with tocilizumab (56-58) There are reports of using rituximab (anti CD-20 monoclonal antibody which inhibits B cell-mediated immune response) and IL-1 inhibitors such as canakinumab and anakinra for NBD (1). Based on activation of the TH 17 pathway in NBD, drugs blocking the TH 17 pathway such as ustekinumab, secukinumab can potentially be useful in this condition. However, data on ustekinumab and secukinumab is limited to BD with peripheral disease manifestations at this time. Ustekinumab is a fully human monoclonal antibody directed against the common shared p40 subunit of IL-12 and IL-23, inhibits their binding capacity to their receptor 12Rβ1, thereby blocks the downstream molecular signaling of IL-12-23, which inhibits the IL-17 pathway. It has been used successfully in BD with oral ulcers with a decrease in plasma levels of IL-17 (59-61). One case report of BD with multisystem involvement including musculoskeletal, ocular, mucosal, and articular involvement, with an overlap of psoriasis vulgaris and hidradenitis suppurativa, was successfully treated with ustekinumab (62).

Secukinumab, IL-17A inhibitor, has been

used in a small number of patients with BD for mucocutaneous and musculoskeletal manifestations successfully (52). Further understanding of immunopathogenesis of NBD may help to decipher distinct pathways to reduce inflammation in this disease and thereby add to the armamentarium against NBD.

CONCLUSION

The immunopathogenesis of NBD is still incompletely understood. However, CSF findings in NBD, indicate both innate and adaptive immune mechanisms are implicated in the pathogenesis of the disease. TH-1 and TH-17 pathways are the major mediators of nervous system inflammation in NBD. TH2 and Treg pathways may have some anti-inflammatory effects and check the ongoing damage in NBD as shown in some studies. IL-6, an inflammatory cytokine that stimulates the TH-17 pathway, may help in the diagnosis of progressive NBD and discrimination of active vs inactive disease. Many other inflammatory cytokines belonging to the TH1 and TH17 pathways are elevated in the CSF in NBD. However, further studies are needed to understand the specificity of those changes compared to other inflammatory neurological diseases to be useful for diagnostic purposes. The CSF findings are also a potential clue to determine therapeutic strategies in NBD. Based on high levels of inflammatory cytokines TNF-alfa, IL-6, TNF inhibitors, and IL-6 inhibitors have been successfully used in NBD in small numbers. These are exciting progress in the field of NBD, a rare, complex, and often life-threatening inflammatory condition. Further research is needed directed towards the determination of accurate diagnostic and prognostic markers and clinical trials for therapeutic strategies in NBD.

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