13th International Conference for

Behçet’s Disease

Epidemiology • Pathogenesis • Clinical Findings • Management • Prognosis

May 24-27, 2008
Pörtschach / Klagenfurt (Austria)
How to reach Pörtschach / Klagenfurt

By plane you may reach Klagenfurt Airport directly from Berlin, Cologne, Düsseldorf, Frankfurt, Hamburg, Hannover, Leipzig, London, and Vienna.

Venue:
Congress Center Wörthersee
Hauptstraße 203, 9210 Pörtschach am Wörthersee, Austria
13th ICBD

May 24~27, 2008
Congress Center Worthersee
Pörtschach / Klagenfurt Austria

140 papers
- Oral presentation-Scientific sessions (26)
- Poster presentation (94)
- Keynote lecture/ Plenary lecture (5)
- Update study group (15)

Meet the professor
- dermatology, neurology, rheumatology

Controversial discussion, Open for discussion
Main Topic

* Epidemiology (14)
* Pathophysiology and basic research (32)
* Clinical manifestations (28)
* Disease assessment, laboratory tests and imaging (14)
* Clinical studies and treatment strategies (11)
* Pediatric manifestations (5)
* Oral, genital, and skin manifestations (12)
* Ocular manifestations (13)
* Manifestations of the central nervous system (8)
* Patients’ education (1)
# Presentations

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Plenary Lectures

1. Infections and immunosuppression (W. Graninger)
2. BD and central nervous system (A. Al-Araji)
3. Endothelium and thrombophilia (F. Espana)
4. BD at the pediatric age (I. Kone-Paut)
5. New perspectives for BD (H. Yazici)
Validation of the International Criteria for BD in Germany, China, Iran, Spain (sensitivity, specificity, accuracy)
FIGURE 167-2  Revised International Criteria for Behçet’s Disease (International Team for the Revision of ICBD; coordinator: F. Davatchi) according to (A) the classification tree format, and (B) the traditional format. ABD = Adamantiades-Behçet disease; GU = genital ulcer; OA = oral aphthous ulcer. (From Zouboulis CC et al: Evaluation and revision of the International Criteria for Behçet’s Disease (ICBD). Abstracts of the 21st World Congress of Dermatology, Buenos Aires, Argentina, 2007, in press, with permission.)
Epidemiology-2

- Change in incidence of pathergy phenomenon in Behcet’s disease over the time
- HLA-B5(1) and risk of Behcet’s disease: A meta-analysis of genetic association studies
Epidemiology-3

HLA-B27 in BD, 5567 patients in Iran
- Positive: 481 patients (8.6%)
  Odds ratio compared to the normal (3.69)
- Ankylosing spondylitis, chronic diarrhea, false positive VDRL, Type III and IV WHO glomerulonephritis

HLA-B51 in BD, 1164 patients in Iran
- Positive: 540 patients (46.4%)
- Favored some manifestations
  : Pathergy reaction, EN, joint manifestations, myocardial infarction, arterial thromosis
- Not clinically as important to use it for any decision making
**Gene**

- **HLA Class I phenotype**
  - Positive correlation: HLA-A2, B5, Bw4, Bw6
  - Negative correlation: HLA-A1, A3, A9, A10, A28, A29
  - HLA-B51: a prognostic indicator for a possible severe eye involvement, esp in male Behcet’s disease patients

- **HLA-A2/B51 combination related to genital lesion**
  - Significant relationship between HLA-A26 locus and ocular lesions

- **IL-18 promoter polymorphism**
  - Susceptibility to Behcet’s disease, esp to mucocutaneous form
**NODs single nucleotide polymorphisms**

- **NOD** (nucleotide-binding oligomerization domain): related with the innate immunity and inflammatory control.
- Two of three NOD2 variant alleles associated with Crohn’s disease are significantly less present in BD compared to healthy controls.
  -> The variant alleles might protect BD.

**P Selectin glycoprotein ligand-1 (PSGL-1) variable number of tandem repeats (VNTR) polymorphism**

- **PSGL-1**: important adhesion molecule involved in lymphocyte recruitment.
- Increased risk of thrombosis in patients with anti-phospholipid antibody syndrome.
- Contribute to the thrombotic tendency observed in patients with BD.
IFNAR1 and IFNAR2 polymorphisms in patients with BD
- IFNAR1, IFNAR2 polymorphisms were disclosed to confer susceptibility to multiple sclerosis characterized by Th1 polarization
- BD patients had a significantly higher frequencies of the genotypic combinations of IFNAR1 and IFNAR2 polymorphisms
  -> jointly but not individually, may confer susceptibility to BD

CTLA-4 gene polymorphisms
- **CTLA4**
  - Co-stimulatory molecule expressed on activated T cells
  - Plays a key role of inhibitory regulator of the T lymphocyte activation
- SNPs of promoter region on CTLA4 gene have a candidate predisposing to BD
- The CTLA4-1722T>C polymorphism may contribute to the clinical useful marker of BD with ocular lesion
**Cell**

- **Endothelial progenitor cells (EPCs)**
  - A subtype of BM-derived progenitor cells expressing surface antigens of both hematopoietic stem cells and endothelial cells: maintenance of vascular integrity and neoangiogenesis
  - Severe reduction of circulating EPCs in BD -> impaired endothelial recovery -> vascular damage

- **RBCs**
  - EM changes in RBCs of BD patients:
    - increased proportions of non-discocytic erythrocytes
    - reduced deformability -> impair blood flow, endothelial dysfunction, tissue hypoxia

- **PMN cells**
  - Elevated serum MPO in BD -> increased activation of PMN, increased production of free radicals, LDL oxidation-> oxidative stress
  - Decreased serum lactoferrin -> impaired antioxidant defense
Cytokine

- IL-12, IL-6, IL-8, IL-17
- IL-6 siRNA injected symptomatic BD mice
  - Downregulate IL-6, decreased severity score, upregulated Foxp3+ Treg cells
- Impaired interferon-beta production from plasmacytoid dendritic cells in patients with BD after CPG-ODN stimulation

Infections

- Oral streptococci
  - Bes-1 DNA and HSP-65 derived from *S. sanguinis* (previously called as *S.sanguis*) in mucocutaneous lesions of BD patients
  - Bes-1 gene: highly homologous with the peptides of human HSP-60
  - HSP-65 and HSP-60: high homologies to T cell epitope
  - -> proinflammatory Th1 type cytokine production
Antimicrobial peptides

CSA-13
- Antimicrobial cationic steroid mimic
  - functions against harmful bacterial infections
  - suppressive effect to vascular morphogenesis
  - treatment of hyper-progressive ocular vasculitis

Human neutrophilic peptide (HNP) 1-3, LL37, S100
- Salivary HNP 1-3 levels were significantly higher in patients with BD
  - associated with severe organ involvement
- Salivary LL37 and S100 levels seemed to be higher in BD
  - correlated with the frequency of oral ulcers and plaque index score reflecting microbial plaque accumulation
- Salivary levels of HNP 1-3, LL-37 and S100 might be related to disease severity, oral ulcer activity and oral infection focuses in BD.
Toll-like receptor (TLR)
- TLR expression (TLR 1, TLR2, TLR3, TLR4, TLR9) at rest and after stimulation, in T cells and monocytes from patients with BD did not differ from that of healthy individuals
- TLR signaling is not impaired in patients with BD

TLR and VitD
- Higher expression of TLR2 and TLR4 in the monocytes of active BD
- Serum 25(OH)VitD was lower in active BD.
- VitD3 dose-dependently suppressed the expressions of TLR2 and TLR4.
  -> VitD: may be a therapeutic option in BD

TLR and Heme oxygenase (HO)-1
- Reduced expression of HO-1 in PBMC from active BD
- Increased expression of TLR4 in PBMC from BD
  -> Microbial pathogen stimulate the innate immune system through TLR4 in PBMC
  -> Defective HO-1 expression contribute to augmentation of inflammation
EGFR and its ligands in buccal swabs
- Not increased secretion of EGF and TGF-a in BD patients with active oral ulcers
- High expression of EGFR during remission
- Downregulated expression of EGFR during active ulcerations

Killer immunoglobulin-like receptor (KIR)
- HLA-B51 express the Bw4 epitope that can bind to a group of polymorphic receptors (KIR) expressed on NK cells and cytotoxic T cells.
- KIR3DL1/S1 allelic association with BD
  -> HLA-KIR interaction is involved in the development of BD.

Soluble endothelial protein C receptor (EPCR)
- EPCR was discovered at the surface of endothelial cells, binds protein C, and enhances its activation.
- Soluble EPCR was also detected in plasma.
- Plasma sEPCR was significantly higher in patients with BD
**Disease activity marker**

**Adiponectin**
- Adiponectin from adipose tissue: *antiinflammatory effect*
  - Decreases expression of adhesion molecules
  - Inhibits attachment of active macrophage to endothelial surface
- Serum adiponecin levels were high during both active and inactive stage in patients with BD.

**B-cell activating factor of the TNF family (BAFF)**
- Polarization of T lymphocytes toward the Th1-type
- Serum BAFF was associated with increased disease activity in BD.
  -> useful marker for the disease activity and potential therapeutic target

**Homocysteine**
- Independent risk factor for venous or arterial thrombosis in Iranian patients with BD
- Negative correlation between HLA-B51 and serum homocysteine
Rebamipide (Mucosta®)
- Improve the efficacy of colchicine for the herpes simplex virus-induced inflammation in a BD mouse model

Rituximab (anti-CD20 monoclonal antibody)
- Reduce macular edema on fluorescein angiography and optical coherence tomography

N-acetyl cysteine as an adjuvant therapy
- No additional benefit on disease activity

The effect of immunosuppressive treatment on skin pathergy reaction
- Colchicine, azathioprine, cyclosporine, or interferon-alpha 2b does not affect the skin pathergy reaction.
Treatment Strategies-2

- **Treatment of sight-threatening panuveitis**
  - Single infliximab infusion has a faster beneficial effect than intravitreous triamcinolone or high dose intravenous methylprednisolone.

- **Combination therapy** of pulse cyclophosphamide, azathioprine, and prednisolone is **the best choice in ocular BD**
  - 1000mg cyclophosphamide in 500 ml serum saline 5% once monthly, 2-3mg/kg azathioprine daily orally, 0.5mg/kg prednisolone daily orally

- **Mycophenolate sodium (case report)**
  - A good therapy before using biologicals or chemotherapeutics in therapy-refractory BD patients with severe ileo-colitis.
Oral, Genital and Skin manifestations

Clinical feature
- Pemphigus vulgaris misdiagnosed as aphthae
- BD mimickers: recurrent aphthous stomatitis, pemphigus vulgaris, erosive lichen planus, bullous pemphigoid, herpes simplex, erythema multiforme, fixed drug eruption, drug eruption, candidiasis, mechanical ulceration, psoriasis, SLE, vasculitic ulceration
- Index for oral ulcer activity: VAS pain score
- Oral ulcer activation after dental and periodontal treatment
- Case report: EM, Cutaneous PAN

Therapy
- Sublingual IFN-a tablet: effective
- Topical tacrolimus for mucosal lesion: effective
- Tropical Nigella sativa 100% oil: safe and effective for RAS
- Zinc sulphate 5% mouthwash: effective, prophylactic for RAS
- Bifidobacterim lactis DN-173 010 strain: effective
Eye involvement and treatment-1

Clinical feature

- Pathergy reaction on conjunctiva after intravitreal TA injection
- A specific finding of Behcet’s uveitis: inferior peripheral pearl-like precipitates
- The risk factors of blindness in Behcet’s disease: higher frequency of uveitis, longer duration of uveitis, retinal vasculitis, initial low vision

Therapy

- Intravitreal TA injection: effective for the suppression of recurrent ocular inflammation, but high frequency of complications
- Interferon-alfa vs cyclosporine in ocular BD: long-term remission and better final visual acuity in IFNa compared to CyA
- Cyclophosphamide pulse therapy: effective for treatment of severe ocular involvement like posterior segment uveitis or panuveitis in BD
- N-acetyl cysteine as anti-oxidant therapy: effective as alternative therapy, but not conclusive
Chemokine environment of intraocular lymphocytes in BD uveitis

- **Aqueous humor of non-BD**: CD4+ cells → high expression of CXCR3
- **Aqueous humor of BD**: CD8+ cells, high expression of IL-8, IP-10

TNF-alpha level in BD patients with and without ocular involvement

- Serum TNF-alpha level is higher in BD patients with ocular involvement

Osteopontin (OPN)

- Acidic phosphoglycoprotein, contains arginine-glycine-aspartic acid cell-binding sequence in extracellular matrix
- Act as a cytokine contributing to the development of Th1 immunity
- Experimental autoimmune uveoretinitis (EAU): a model for human intraocular inflammation such as BD

-> EAU was ameliorated in OPN-deficient mice and wild type mice treated with OPN neutralizing antibody or OPN-siRNA
Neurologic involvement and treatment

Clinical feature
- Recurrent meningitis, pseudotumor cerebri
- Neurologic manifestation of BD in USA, Japan, Turkey
- Symptom Check List 90-Revised in BD: SCL 90-R was unable to detect major psychological symptoms in BD.

Therapy
- Infliximab for chronic progressive neuro-BD: effective treatment by reducing CSF IL-6 levels, smoking might be one of resistance factors to treatment.
- Interferon-alpha 2a: effective in refractory juvenile BD with CNS involvement
Vascular involvement

- Large vessel involvement
  - Aortic and peripheral arterial involvement at an older age compared to pulmonary artery aneurysm and venous involvement, not associated with venous lesions
- Intracardiac thrombosis
- Pulmonary artery aneurysm
- Coronary artery aneurysm
- Vascular involvement of the intra-abdominal organs
  - SVC obstruction, IVC obstruction, Budd-Chiari syndrome, mesenteric artery aneurysm, splenic artery thrombosis, mesenteric artery occlusion, pulmonary embolism
Other involvement

- Sacroilitis and HLA B27
  - not increased in BD

- Thyroid disorders
  - Graves’ disease, Hashimoto’s thyroiditis, thyroid nodule, diffuse goiter

- Renal involvement
  - Renal lithiasis, amyolodosis, CRF, hematuria, arterial hypertension, renal TB

- Chylothorax and chylopericardium

- Sjogren’s syndrome

- Comorbidities in BD
  - diabetes mellitus, renal disorder, malignancy

- Malignancy
  - BCC, rectal adenocarcinoma, lung cancer
Disease assessment

- **Intima-media thickness (IMT) of carotid artery in BD**
  - Thinning of IMT: risk factor of aneurysm formation

- **Increased carotid arterial stiffness (augmentation index: AI) and thickness (IMT) in BD**
  - Independent predictors of elevated cardiovascular risk

- **Reduced pressure wave reflections (low AI) in active BD**

- **PPD reaction is not augmented in BD**
  - not affected by the pathergy reaction

- **Nailfold capillaroscopy In BD**
  - Nail fold abnormality, mainly enlarged capillaries are frequent in BD. These may be related to superficial phlebitis or high blood pressure.
HULUSI BEHCET AWARD
6. Election of the new members of the Executive Committee

- Secretary: Prof. Dongsik Bang (Korea)
- Treasurer: Prof. S. Assaad Khalil (Egypt)
- Member for Scientific affairs: Prof. Haner Direskeneli (Turkey)
- Ordinary members: Prof. Eun So Lee (Korea); Prof. Petros Sifikakis (Greece)
The 14th ICBD
- United Kingdom (London)
- July 7-10, 2010
- President: Prof. Dorian O Haskard F
Thank You!!