Poster Presentations 17th International Conference on Behçet’s Disease

P124.

IMMUNOLOGICAL PROFILING OF AQUEOUS HUMOR IN BEHÇET’S DISEASE PATIENTS WITH ACTIVE OCULAR INVOLVEMENT

Soriano A.1, Croci S.2, Camino L.2, Fontana L.1, Bonacini M.2, Zerbini A.2, Parmeggiani M.1, Salvareni C.1

1Rheumatology Unit, Arcispedale Santa Maria Nuova – IRCCS, Reggio Emilia, Italy; 2Unit of Clinical Immunology, Allergy and Advanced Biotechnologies, Arcispedale Santa Maria Nuova – IRCCS, Reggio Emilia, Italy.

Background. Behçet’s disease (BD) is a systemic inflammatory disorder whose clinical hallmark are recurrent oral and genital ulcers, variably associated with various organ involvement. Uveitis and retinal vasculitis are among the most common manifestations, occurring in 60-80% of patients during the disease course. The pathogenesis of BD is still unclear. Some HLA-I residues have recently been shown to influence antigen binding and regulate the activation of both Natural Killer (NK) cells and CD8+ cytotoxic T lymphocytes. Higher levels of Natural Killer T (NKT) cells (CD3+ CD56+) have previously been found in the aqueous humor (AH) of patients with BD-related uveitis as compared to other types of uveitis. The aim of our study was to perform an immunological profiling of AH in BD patients with active uveitis, comparing it to that of AH from patients with active Vogt-Koyanagi-Harada (VKH) disease and subjects with cataract undergoing surgery.

Patients and Methods. AH of 8 adult patients with BD (according to 1990 DGB criteria) and active uveitis, and of 8 patients with active VKH were analyzed. Patients were defined as having active uveitis when a 2 cells in the anterior chamber (Hogan scale, 1950), and/or 2+ vitritis (Nussenblatt scale, 1990), papillitis, macular edema supported by optical coherence tomography and retinal vasculitis with active ‘photo fundus’, were found. AH from 5 subjects undergoing cataract surgery were included as controls. Cytokine levels were determined by flow cytometry using anti-CD3, -CD56, -CD16 antibodies.

Preliminary Results. Levels of IL-β, IL-1RA, IL-5, IL-7, IL-6, G-CSF, IFN-γ, IFN-α, TNF-α were determined in AH from BD and VKH patients, but not in the control group. Lower levels of GM-CSF were found in BD and VKH patients as compared to controls. No differences were detected between BD and VKH patients regarding cytokine levels. However, HA from 4 BD patients showed a peculiar distinct pattern in terms of cytokine levels, when analyzed by unsupervised cluster analysis. The frequency of NKT cells (CD3+ CD56+) was significantly increased in BD patients as compared to VKH, while that of NK cells (CD56+ CD56neg) and T cells (CD56neg CD3+ was similar. Finally, no difference was found between NKT and NK subsets in terms of proportion of CD16+ cells in both BD and VKH groups.

Discussion. Our preliminary results confirm the previous observation of increased NKT cells levels in BD uveitis as compared to VKH. In addition, AH of both BD and VKH groups showed increased levels of IL-6, G-CSF and IFN-γ, which might suggest their potential role in the immune-pathogenesis of those types of uveitis. A distinct cytokine profile able to distinguish the two conditions remains to be identified.

References


Epidemiology and Genetics

P18.

HLA REVISITED IN EGYPTIAN PATIENTS WITH BEHÇET’S SYNDROME: NEW ASSOCIATIONS OF HLA ALLELES WITH SUSCEPTIBILITY, PROTECTION, PRESENTATION AND SEVERITY OF THE DISEASE

Elshawi M.1, Elgengehy F.1, Mostafa G.2, Elshawi S.1, Elshawi M.1, Youssaly I.1

1Kasr Alainy Hospital, Cairo University; 2Department of Rheumatology, Egypt.

Background. Behçet’s disease is a multisystem autoimmune syndrome. Its manifestations usually start in the young adulthood affecting mainly the skin, eyes, Brain and blood vessels (1).

Objectives. The aim of the study was to perform HLA class I genotyping in a cohort of Egyptian patients with Behçet’s syndrome and comparing them with HLA genotyping in healthy population (control group) to estimate the syndrome susceptibility and possible association between HLA and syndrome presentations.

Methods. Fifty-seven Egyptian patients with Behçet’s syndrome fulfilling the International study group criteria for Behçet’s syndrome (2) were recruited from the Rheumatology department, Cairo University teaching hospitals. HLA class I genotyping was done for all patients via sequence specific oligonucleotides probes at the National Cancer Institute. HLA class I genotyping data of normal control group was obtained from case control studies done on Egyptian population with a total of 221 individual (3-4).

Results. The studied 57 patients were divided into 50 males and 7 females. The mean age of patients was 35.28 ± 9.73 years with mean disease duration of 9.21 ± 7.36 years. The main clinical features were oral ulcers (100%), genital ulcers (100%), eye involvement (54%) neurological involvement (29%) and vascular involvement (36%) furthermore (33%) had bilateral visual acuity ≤60/60 fulfilling the diagnosis of legal blindness. Certain HLA genotypes were significantly associated with susceptibility for Behçet’s syndrome, the odds ratio (OR) for HLA-A68 was 8.4 (CI=2.9-25.9), HLA-B15 was 6.7 (CI=2.9-15.6), HLA-B51 was 0.6 (CI=3.4-13.0), HLA-A24 was 4.0 (CI=1.5-10.2) and HLA-A2 was 2.1 (CI=1.3-3.8). On the other hand HLA A3 genotype was found to be significantly protective with odds ratio of 0.003(CI=0.01-0.06). HLA B51 was significantly associated with ocular disease with odds ratio of 3.47. Furthermore HLA B51 was associated with legal blindness with a significant odds ratio of 5.21.

Conclusions. HLA A68, B15, B51, A24 and A2 are associated with Behçet’s syndrome susceptibility in the present cohort of Egyptian patients and A3 was found to be protective. HLA B51 is associated with ocular involvement and more important the blinding eye disease and can be considered as a poor prognostic marker for ocular disease.

References

1. YAZICI H, SEYAH E, YURDAYLIK S

P20.

HLA-B5/51 GENOTYPE: AN ASSOCIATION WITH THE CLINICAL MANIFESTATIONS OF BEHÇET’S DISEASE

Ismailova F.1, Kadare M.2, Alekperova Z.2

1V.A. Nasonova Research Institute of Rheumatology, Moscow, Russia, 2Dagestan State Medical Academy, Makhachkala, Dagestan Republic, Russia.

Objective. To estimate the contribution of HLA-B5/51 genotype to the clinical manifestations and risk of Behçet’s disease (BD) in two ethnic groups.

Subjects and methods. 146 BD patients fulfilling the International Criteria for BD (ICBD) were divided into two ethnic groups: 1) 86 patients from Dagestan (representatives of 8 ethnic nationalities in this region) with mean age 30.749 ± 8 years; disease duration – 8.8 ± 10.1 years; 2) 60 ethnic Russian patients, nonresidents of Dagestan with mean age 32.9 ± 11.1 years; disease duration – 11.2 ± 10.1 years. All patients were examined at the V.A. Nasonova Research Institute of

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P21. DETERMINATION OF METHYLATION AND EXPRESSION OF IL-10 GENE IN PATIENTS WITH BEHÇET’S DISEASE

Khabbazi A., Alipour S., Farhadi J., Sakhinia E.
Connective Tissue Diseases Research Center, Internal Medicine Department, Tabriz, Iran

Behçet’s disease (BD) is an autoimmune disease which is described by recurrent aphthous stomatitis, ulcers, genital ulcers, and skin lesions. Variation in the methylation of Interleukin-10 (IL-10) gene have been proven in the pathogenesis of inflammatory diseases but it was not studied in Behçet’s disease. Therefore the goal of this study was to measure the methylation level of IL-10 in patients with BD compared to the control group and to determine the expression of this gene in the two groups. In this study, blood samples from 40 patients and 40 healthy control were taken, with the mononuclear cells isolated with ficoll protocol. The DNA and RNA were then subsequently extracted. Following this, the extracted DNA was converted to cDNA using the RT-PCR method, with the expression of IL-10 later evaluated by Real-time PCR. As we expected, the expression level of this gene was significantly decreased in the patient group compared to the control. Also in this study, the methylation of IL-10 was measured by MeDIP (Methylation DNA Immunoprecipitation) technique and since methylation of promoter regions have inhibitory effects on gene expression, the rate of methylation increased in this gene and hypermethylation. According to these results, we suggest that hypermethylation of promoter regions of IL-10 can affect the regulatory regions and eventually it plays a role in the pathogenesis of Behçet’s disease.

P22. TRANSITION OF CLINICAL MANIFESTATION IN JAPANESE PATIENTS WITH BD


1Yokohama City University Graduate School of Medicine, Stell Cell and Immune Regulation Department, Yokohama City, Japan; 2Yokohama Minami Kyo-sai Hospital, Yokohama City, Japan; 3Yokohama City Hospital, Yokosuka, Japan; 4Chigasaki City Hospital, Chigasaki, Japan; 5Yokohama University Hospital, Yokohama City, Japan; 6Yokohama City Hospital, Yamanashi, Japan; 7University of Tokyo, Japan; 8National Hospital Organization Yokohama Medical Center, Yokohama City, Japan; 9Nippon Medical School Graduate School of Medicine, Tokyo, Japan

Objective. To evaluate phenotype transition of Behçet’s disease after the publication of retrospective study of 412 patients by Ideguchi et al in 2007.

Methods. We retrospectively analyzed 578 patients, who fulfilled 1987 Diagnostic Criteria of the Behçet’s Disease Research Committee of Japan. Presence of clinical manifestations as oral ulcer, genital ulcer, etc, HLA-B51 positivity, observation period, date of diagnosis, and rate of complete type (patients having all eye, oral ulcer, skin rash, and genital ulcer) were selected as variables. We further divided the patients into three groups based on the year of diagnosis (before 2000, 2000-2007, and after 2008) and analyzed their phenotypes.

Results. The patients’ characteristics of the study were as follows: female n=331, male n=247, average of disease onset, 36.8±12.4 y.o, frequency of oral ulcer 99.0%, genital ulcer 72.3%, ulcers 61.6%, skin involvement 88.8%. As previously shown, rate of ulcers and neuro type were significantly higher in male, whereas rate of genital ulcer, arthritis were higher in female. After the adjustment of observation period, we performed Cochran–Armitage test to evaluate the transition of disease phenotypes. The result showed significant decrease of complete type, genital ulcer, and HLA-B*51 positivity, whereas increase of gastrointestinal disease.

Conclusions. We found continuous transition of Behçet’s disease phenotypes in Japanese patients.

P23. ASSOCIATION OF GENETIC POLYMORPHISMS IN INTERFERON-Γ, INTERLEUKIN-6 AND TRANSFORMING GROWTH FACTOR-B1 GENE WITH BEHÇET’S DISEASE SUSCEPTIBILITY

Al-Okaify F., Al-Rashidi S., Al-Balawi M., Arfin M., Al-Asmari A.
Prince Sultan Military Medical City Riyadh, Rheumatology Department, Riyadh, Saudi Arabia

Behçet’s disease (BD) is a chronic relapsing, multisystem inflammatory disease characterized by recurrent oral and genital mucous ulcers, and ocular and skin lesions. Cytokines play an important role in the pathogenesis and disease progression of BD. The aim of this study was to investigate the impact of gene polymorphisms of TNF alpha cell subtype Th1 and Th2 cytokines, interferon-gamma (IFN-γ), interleukin-6 (IL-6) and transforming growth factor (TGF)-β1 on BD susceptibility in a Saudi cohort. Sixty-seven unrelated patients with BD and 195 healthy controls were genotyped for IFN-γ (874A/T), IL-6 (174G/C) and TGF-β1 (509C/T) polymorphisms. Genomic DNA was extracted from the peripheral blood of BD patients and controls using Qiagen RDX mini kit (Qiagene, Hilden, Germany). IFN-γ gene was amplified using amplification refractory mutation systems (ARMS)-PCR methodology to detect polymorphisms at position 874 of IFN-γ. The TGF-β1 (509C/T) and IL-6 (174G/C) polymorphisms were detected by PCR- restriction fragment length polymorphism (PCR-RFLP) technique. The frequency of genotype AT of IFN-γ (874A/T) was significantly higher while genotype AA was lower in BD patients as compared to controls (p<0.05). The frequency of T containing genotypes (AT+TT) was also higher in BD patients compared to that in controls (p=0.02). The frequencies of allele T and A were not statistically different in patients and controls (p=0.31). There was no significant difference in the frequencies of alleles and genotypes of IL-6 (174G/C) and TGF-β1 (509C/T) polymorphisms between patient and control groups. These results indicated that genotype AT of IFN-γ (874A/T) polymorphism is associated with BD risk and genotype AA is protective to BD. On the other hand the polymorphisms IL-6 (174G/C) and TGF-β1 (509C/T) may not be associated with BD risk in our population. It is concluded that IFN-γ (874 A/T) polymorphism is associated with the susceptibility of BD, however further studies with large sample size involving different ethnic populations should be conducted to strengthen these results.

P24. THE PREVALENCE OF BEHÇET’S DISEASE IN NORTH JORDAN

Madanat W., Al-Tamimi A., Alawneh K., Smadi M., Han B., Yazici H.

Jordan’s Friends of Behçet’s Disease Patients Society, Rheumatology Department, Amman, Jordan; 2Department of Medicine, King Abdullah Hospital, Jordan University of Science and Technology, Irbid, Jordan; 3Department of Mathematics and Statistics, Jordan University of Science and Technology, Irbid, Jordan; 4Cerrahpaşa Medical School Hospital – University of Istanbul, Turkey

Introduction. The prevalence of Behçet’s disease (BD) is much higher in countries along the ancient Silk Route than in north Europe and the USA. Here we report the first epidemiological study of BD from another mid-eastern country, Jordan.

Purpose. To estimate the prevalence of BD among hospital workers in Jordan, with the additional aim of comparing this prevalence among hospital workers in other geographies.

Materials and methods. In the first stage of our survey, 2569 Jordanian hospital workers from 6 hospitals in the north of Jordan were interviewed by trained residents, using a screening questionnaire to identify individuals with recurrent oral ulcers (ROU), previous diagnosis of and/or any major symptom related to BD. In the second stage all individuals with ROU or previous diagnosis of BD identified at stage one, who agreed to a further investigation, were examined by two rheumatologists for the presence/ confirmation of BD according to the 17th International Conference on Behçet’s Disease Poster Presentations

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Materials and methods. We recruited 488 Japanese BD patients, 380 Japanese VKH patients, and 1,067 Japanese healthy controls. We genotyped four single nucleotide polymorphisms (SNPs) (rs6540679, rs10863888 and rs12509232 in TRAF5 and rs13210247 in TRAF3IP2) assessed in the previous study using TaqMan assay.

Results. Of the four SNPs, rs13210247 in TRAF3IP2 showed a significant association with BD (p=0.048), and the G allele of rs13210247 had an increased risk of BD (OR=1.53); this finding is in line with the previous study in a Han Chinese population. The other three SNPs were not significantly associated with BD risk. For VKH, rs6540679 in TRAF5 showed a significant association (p=0.0039), and the A allele of rs6540679 had an increased risk of VKH (OR=1.30), whereas the A allele served a protective role in VKH cases of previous study. The other SNPs did not show any significant association with VKH.

Conclusions. We found that rs13210247 in TRAF3IP2 contributes to the risk of BD in both the Japanese and Han Chinese populations, suggesting that TRAF3IP2 is an important genetic susceptibility factor to BD, and functional studies are needed to clarify the contribution of TRAF3IP2 to the development of BD.

P27.

PREVALENCE OF BEHÇET’S DISEASE AND OTHER UVEITIC CONDITIONS IN SECONDARY EYE CARE: A PRELIMINARY STUDY

Fehim Esen
Devrek State Hospital, Ophthalmology Clinic, Zonguldak, Turkey

Objective. The aim of this preliminary study was to document demographic and clinical features of uveitis patients in secondary care setting.

Methods. Uveitis patients who presented at Devrek State Hospital Ophthalmology Clinic between September 2015 and April 2016 were prospectively recorded. Patients were classified as acute idiopathic anterior uveitis (n=5), ankylosing spondylitis (n=3), Fuchs uveitis (n=1), idiopathic panuveitis (n=1) and intermediate uveitis (n=1).

Results. Between September 2015 and April 2016, 7,536 eye examinations were performed at the ophthalmology clinic (the only eye care center in Devrek district) and 31 of these visits were related with uveitis (0.41%). Fourteen patients (mean age: 37.8±18.5, 5 male, 9 female) were diagnosed with uveitis and among them only 3 cases were diagnosed with Behçet’s Disease (BD). Other diagnoses were acute Glaucoma (n=1), chronic uveitis (n=2), Fuchs uveitis (n=1), idiopathic panuveitis (n=1) and intermediate uveitis (n=1).

Conclusion. The prevalence of Behçet’s disease was reported as 32.1% among uveitis patients in a previous, multicenter tertiary care center study in Turkey. This pilot study indicated a relatively lower prevalence of BD in secondary care setting (21.4%), while BD patients represented 60% of the cases referred to a tertiary center. There may be a referral bias for overrepresentation of BS cases in tertiary uveitis centers.

P28.

BEHÇET’S DISEASE: ETHNOS AND FAMILIAL AGGREGATION

Aleksyeva Z.1, Izmailova F.1, Kudaev M.2, Denisov L.1, Nasonova E.1
1V.A. Nasonova Research Institute of Rheumatology, Moscow, Russia; 2Dagestan State Medical Academy, Makhachkala, Dagestan Republic, Russia.

Objective. To study the prevalence of familial aggregation in patients in three ethnic groups: Dagestanians, Chechens and Russians.

Materials and methods. 180 BD patients (proband) who were observed as out-patients and in-patients were questioned within the period of 2011-2014. Distribution of pts according ethnic indication: 86 dagestanians, 34 chechens and 60 Russians. Diagnosis of BD was done according ICCBD criteria (1990). Average age of pts- 30.7±9.6 yrs, disease duration 8.8±10.1 yrs. Genealogical tree of probands for symptoms of BD in relatives was determined by questionnaire. Pts could definitely name only the presence of recurring stomatitis among their relatives.

Results. Cases with recurring aphthous stomatitis (RAS) were found in 54 families: among Dagestanians in 37%, Chechens in 22%, Russians 18%. Repeated cases of RAS in families: father-13, mother-11, siblings: brother-13, sister-8, son-2, daughter-7 in siblings, RAS was met more often than in other relatives. In 13 probands with BB cluster variants of familial aggregation were found- in three families RAS was found: mother-brother-uncle; mother-daughter; father-brother-uncle.

Conclusion: the strong association has been confirmed in different relatives with RAS who should be included in the risk group on BD.
P29.

THE CORRELATION OF PREFECTURAL PREVALENCE OF BEHÇET’S DISEASE WITH CIGARETTE SMOKING RATE IN JAPAN

Kono H., Asako K., Kikuchi H.
Teikyo University School of Medicine, Internal Medicine Department, Kawasaki, Kanagawa, Japan

Introduction. It is not well known that whether cigarette smoking is associated with pathogenesis of Behçet’s disease. Smoking was previously shown to be associated with chronic progressive neurological manifestations of Behçet’s disease. On the contrary, smoking was reported to have a favorable effect on mucocutaneous symptoms of Behçet’s disease.

Patients and methods. The prevalence of Behçet’s or other systemic autoimmune diseases in each of 47 prefectures of Japan is obtained by the registration system of The Ministry of Health, Labour and Welfare (MHLW) Research Project for the Treatment of Intractable Diseases from 1974 to 2014. The smoking rate of adults in each prefecture is obtained by the Comprehensive Survey of Living Conditions by MHLW.

Results. Total number of the registered Behçet’s patients in Japan of 2014 was 20,035 (female 11,449) and the point prevalence was 158 patients per million. The prevalence of each prefecture varies from 101 to 240 patients per million. The prefectural prevalence of Behçet’s disease is correlated with the smoking rate of adults (p=0.00021). The smoking rate does not correlate with the prefectural prevalence of other systemic autoimmune diseases including SLE, MCTD, GPA, MPA (+PN), Takayasu arteritis or RA with vasculitis. The annual incidence of Behçet’s disease in Japan did not show a clear trend from 1974 to 2014; on the other hand, smoking rate has been continuously dropping during this period.

Discussion. The cross sectional data indicated that the prefectural rate of cigarette smoking is associated with prevalence of Behçet’s disease in Japan. Of note, the data are not enough to support the cause and effect relationship of smoking and Behçet’s disease. The shown relationship can be casual, or be mediated by unknown confounding factors.

P30.

BRITISH PAEDIATRIC SURVEILLANCE UNIT (BPSU) STUDY OF BEHÇET’S SYNDROME IN CHILDREN AND YOUNG PEOPLE IN THE UNITED KINGDOM

Pain C.1, Rice H.1, Beresford M.2, Brogan P.3, Fortune F.4, Moots R.5, Murphy R.6
1Alder Hey Children’s NHS Foundation Trust, Paediatric Rheumatology Department, Liverpool, UK; 2Institute of Translational Medicine, University of Liverpool & Alder Hey Children’s NHS Foundation Trust, Liverpool, UK; 3Liverpool Ormond Street Hospital, London, UK; 4Queen Mary School of Medicine and Dentistry, London, UK; 5University Hospital Aintree, Liverpool, UK; 6Royal Hallamshire Hospital, Sheffield, UK

Behçet’s syndrome is a rare multi-system inflammatory condition. The disease burden of Behçet’s syndrome in patients under 16 years of age in the UK is not well described. The British Paediatric Surveillance Unit (BPSU; www.rech.ac.uk/bpsu) has a long history of rare disease epidemiological research. Paediatricians in the UK receive monthly alerts to notify any cases they have seen during the previous month. Return rates for BPSU alerts are high at above 90% providing a robust method of identifying incidence and prevalence of rare paediatric disease.

Aims. 1) To identify the incidence and prevalence of Behçet’s syndrome in children under 16 years of age in the UK; 2) To describe clinical manifestations, demographics and patterns of clinical care

Methods. From 1st May 2015, paediatricians in the UK via the BPSU and members of the British Society of Paediatric Dermatologists received monthly email notification forms. Clinicians were asked to report any child up to the age of 16 who had 2 or more of the following features not explained by an alternative diagnosis:

1) Recurrent oral aphthous ulceration
2) Skin involvement
3) Positive pathergy test
4) Eye involvement
5) Gastrointestinal involvement
6) Family history of Behçet’s syndrome in a biological parent or sibling
7) Vascular involvement
8) Neurological involvement

Results. Over the first 11 months, 90 cases have been notified and 28 completed questionnaires analysed (16 cases have been excluded; 8 errors and 8 duplications). Seven of the reporting cases are incident and 21 are prevalent cases. 21 out of 28 cases fulfil the criteria for definite Behçet’s syndrome defined in this study as an ICBD score of four or more. 1 Children have a wide array of clinical manifestations with recurrent oral ulceration being the most common then genital ulceration (67%) and skin involvement (46%). Eye involvement, neurological and vascular involvement were less common (see Table 1). Most children were followed up in tertiary care by a number of different specialties. According to the reporting clinician, over half the patients had their disease controlled on treatment whilst 29% still had active disease despite treatment.

Table 1. Showing demographics, clinical features, management and outcomes of analysed cases (n=28). Numbers in brackets indicate percentages.

**SEX**

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Male</td>
<td>16 (57.1)</td>
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<tr>
<td>Female</td>
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**ETHNICITY**

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<tr>
<td>Any white background</td>
<td>32 (110.3)</td>
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<tr>
<td>White and Black African</td>
<td>2 (6.9)</td>
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<tr>
<td>Indian</td>
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<tr>
<td>Pakistani</td>
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<td>Turkish</td>
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<tr>
<td>African</td>
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**MEAN AGE**

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<tbody>
<tr>
<td>At Presentation</td>
<td>8.95 years</td>
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<tr>
<td>At Diagnosis</td>
<td>9.35 years</td>
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**DISEASE FEATURES**

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<tbody>
<tr>
<td>Oral ulceration</td>
<td>27 (96.4)</td>
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<tr>
<td>Skin involvement</td>
<td>13 (46.4)</td>
</tr>
<tr>
<td>- Erythema nodosum</td>
<td>5 (17.6)</td>
</tr>
<tr>
<td>- Skin ulcers</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>- Pustulosis</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Eye involvement</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>- Anterior uveitis</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>- Intermediate uveitis</td>
<td>2 (7.2)</td>
</tr>
<tr>
<td>- Retinal vasculitis</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Vascular involvement</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Neurological involvement</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Other manifestations</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>- Abdominal pain</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>- Stomach</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>- Arthritis</td>
<td>4 (14.2)</td>
</tr>
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**FAMILY HISTORY**

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<tbody>
<tr>
<td>Sibling/Parent</td>
<td>7 (25.0)</td>
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<tr>
<td>Non-first degree relative</td>
<td>3 (10.7)</td>
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**CLINICAL TEAMS INVOLVED**

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<tbody>
<tr>
<td>Paediatric Rheumatologist</td>
<td>27 (96.4)</td>
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<tr>
<td>Adult Rheumatologist</td>
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<tr>
<td>Ophthalmologist</td>
<td>23 (82.1)</td>
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<tr>
<td>Oral Medicine/ Paediatric Dentist</td>
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</tr>
<tr>
<td>Clinical Psychologist</td>
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<td>Support Worker</td>
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<tr>
<td>Gynaecologist</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Special Nurse</td>
<td>12 (42.9)</td>
</tr>
<tr>
<td>Paediatric Immunologist</td>
<td>5 (17.8)</td>
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**OUTCOMES**

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<tbody>
<tr>
<td>Outcome not known</td>
<td>1 (3.6)</td>
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<tr>
<td>Stable off medication</td>
<td>7 (25.0)</td>
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<tr>
<td>Remission with sequelae</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Controlled on medication*</td>
<td>16 (57.1)</td>
</tr>
</tbody>
</table>

*Of those children controlled on medication, 2 were on topical therapy only and 14 required systemic treatment which included azathioprine and anti-TNF therapies most commonly

Discussion. Study findings are limited at this stage related to the small number of completed cases which have been analysed. Incidence and prevalence rates will be calculated once completed 12 month’s data is obtained. However, case reporting highlights the extreme rareness of Behçet’s syndrome in children within the UK. Comparison of frequency of disease manifestations with non-UK cohorts will be important in future analysis as there may be differences in our UK population, for example a low frequency of ocular involvement. This is important when considering the design of healthcare services that address the needs of children.

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REF The ICBD. J Eur Acad Derm Ven 2014
P31. ARTIFICIAL MANIFESTATION OF BEHÇET DISEASE IN NORTHERN ITALY

Berti A.1, Felicetti M.2, Bortolotti R.3, Cavatorta F.2, Paolazzi G.3
1IRCCS San Raffaele Scientific Institute, Department of Medicine and Clinical Immunology, Milan, Italy; 2University of Padua, Department of Rheumatology, Padua, Italy; 3Santa Chiara Hospital, Department of Rheumatology, Trento, Italy

Purpose. Behçet disease (BD) is a chronic relapsing inflammatory disorder of unknown etiology. We aim to analyze articular involvement in patients with Behçet’s disease (BD) of a regional hospital of Northern Italy.

Methods. We retrospectively collected all patients diagnosed with BD following BD criteria between 1990 and 2016 and followed at the regional hospital S. Chiara, Trento. Data analysis was done by using descriptive statistical indices such as mean and confidence interval. The comparisons were done by hisqure test.

Results. Fifty-nine consecutive patients (43.7% men and 56.3% women) were enrolled. Mean age at disease onset was 39 (range, 22-65) years old, and the observed frequency of HLA-B51 was 73.0% (43/59). Ethnic backgrounds of the patients were reported as follows: 84.1% (48 cases) from Trentino province (TP), 8.5% (5 cases) from other Italian regions different from TP, 6.8% (4 cases) from Northern Africa, 3.4% (2 cases) from the Middle East.

Conclusions. No significant differences were observed between the ethnic groups. The frequency of HLA-B51 was the highest in patients from Trentino, followed by those from Northern Africa and the Middle East. Further studies are needed to confirm these findings.

P32. A DARWINIAN VIEW OF BEHÇET’S DISEASE

Wallace G.1, Smith R.2, Roberts A.3
1University of Birmingham, Institute for Inflammation and Ageing, Birmingham, UK; 2University of Liverpool, Liverpool, UK

Behçet’s Disease (BD) is a multisystem autoinflammatory disease that is prevalent with a specific global distribution between 30° and 45° north across Asia and Europe. The strongest genetic association in BD is the major histocompatibility complex on chromosome 6, specifically HLA-B*51. MHC class I molecules can present peptides to CD8 cytotoxic T cells and control Natural killer cell activity. However, what is not clear is the function of HLA-B*51 in BD. A recent review supports the concept that MHC class I facilitates immune reactions in a tissue-specific manner that may explain BD pathogenesis.

Recently the Neanderthal genome has been sequenced and analysis has shown a specific manner that may explain BD pathogenesis. However, what is not clear is the function of HLA-B*51 in BD. A recent review supports the concept that MHC class I facilitates immune reactions in a tissue-specific manner that may explain BD pathogenesis.

Importantly, this is relevant to BD. Several other SNP in genes including NEK9, TLR7, and TLR9, have been reported to be associated with BD but only in certain ethnic groups. We present here how these genes may influence HLA-B*51 responses and play a role in the pathogenesis of BD.

P33. IMPORTANCE OF LESS SENSITIVE FEATURES TO INCREASE PROBABILITIES OF BEHÇET’S DISEASE DIAGNOSIS

Schirmer M.1, Salehdi Abdollahi B.2, Davatchi F.3, Zouboulis C.4
1Medical University of Innsbruck, Department of Internal Medicine, Clinic V1 (Infectiology/Immunology, Pulmology, Rheumatology), Innsbruck, Austria; 2Tehran University of Medical Sciences, Tehran, Iran; 3Dessau Medical Center, Division of Evidence Based Dermatology, and Departments of Dermatology, Venerology, Allergology and Immunology, Dessau, Germany

Introduction. The new International Criteria for Behçet’s Disease (ICBD) introduced the concept of a plausibility scale for BD. Scoring points +1 and -4 in ICBD suggests very unlikely to possible but not probable diagnosis of Behçet’s Disease (BD). To increase the plausibility of BD-diagnosis in those patients who don’t fulfill the criteria combinations of less sensitive and specific BD-features can be useful. The aim of this study was to design BD-specific probability tables to be used in patients not yet diagnosed as BD according to ICBD criteria.

Methods. Complete international data-set of the ITR-ICBD study, include 2556 BD patients and 1163 controls from 27 countries was used as a sample. Separate calculations were performed for the Silk-Road, Far Eastern, African, and Western clusters. Positive Likelihood Ratios (LRs) of different features were performed for each cluster. Combinations of the LRs for 1- and 0-point features in ICBD were assessed. The results of the combinations were called LR products. Results. The higher LRs leaded to the higher posttest probabilities because the increase of numerator contributed to increase in the quotient of the posttest probability calculation. Conclusion. Combination of LRs for BD-features increased the post-test probability of BD. This study shows the importance of all BD features to diagnose BD and shows the differences of this impact in different areas of the world. Further validation studies may reveal the weakness of current method and improve the estimated probabilities.

P34. BEHÇET’S SYNDROME ASSOCIATED WITH TAKAYASU’S ARTERITIS: A CASE SERIES OF 10 PATIENTS

Esaatoglu S.N., Seyahi E., Ugurlu S., Hatemi G., Melikoglu M., Hamuryudan V., Yurdakul S.
Istanbul University, Cerrahpasa Medical Faculty, Department of Internal Medicine, Division of Rheumatology, Istanbul, Turkey

Background. Behçet’s syndrome (BS) and Takayasu’s arteritis (TA) are both systemic vasculitis of an unknown etiology, each with unique involvement pattern. BS is characterized mainly by recurrent skin –mucosa lesions and uveitis. Arterial involvement is rare in BS and manifests usually as aneurysms or in situ thrombosis. TA affects aorta and its main branches causing narrowing or occlusions. We describe here 10 BS patients with concomitant TA with demographic and clinical characteristics, treatment strategies and outcome.

Methods. We reviewed the charts of patients diagnosed with BS and TA for information regarding patients’ gender, age at diagnosis of BS and TA, manifestations, symptoms prior to TA diagnosis, type of aortic involvement, and the drugs that were used. All BS patients fulfilled the international study group criteria. The diagnosis of TA was based on the finding of typical homogenous arterial wall thickening.

Results. We identified 10 (0.1%) patients among 9000 BS patients. Their mean age at the time of diagnosis of BS was 31.6±11.5 years, and at the time of diag-
nosis of TA was 37.5±10.8. F/M ratio was 7/3. TA preceded BS in 4 cases (6, 12 and 15 years) and occurred simultaneously in the remaining 6. Skin-mucosa lesions were the most common finding, followed by uveitis (6/10), and arthritis (3/10). Initial symptoms of TA were fatigue and fever in 2 patients, absent pulse in 2, fatigue in 2, arm claudication in 1. The remaining 3 patients were diagnosed as TA while being evaluated for the extent of vascular disease for BS. Subclavian (6/10) and carotid arteries (7/10) were the most commonly involved arteries. In addition to prednisolone, the initial agent was methotrexate in 4 patients, azathioprine in 4, and cyclophosphamide in 1. At the end follow-up (1, 2, 2.3, 7, 9, 18, 21, 23 years), 6 patients had a stable disease following the first treatment, 3 had to switch to infliximab and 1 had to switch to azathiprine after methotrexate. By the end of the follow-up, BS manifestations have resolved in 8 patients, while recurrent arthritis persisted in 2. Seven patients were still on immunosuppressive therapy due to TA, while the remaining 3 were off treatment. None had died. Recurrent arthritis persisted in 2. Seven patients were still on immunosuppressive therapy due to TA, while the remaining 3 were off treatment. None had died.

Conclusions. BS may be associated with TA. Similar associations of TA have been reported with ulcerative colitis, Crohn’s disease, and ankylosing spondylitis (1-3). Whether it is a true association or mere co-existence is always debated. Interestingly, in this hybrid setting, both TA and BS followed their own course: while BS abated in time, TA continued its persistent activity.

References

P35.
AN ITALIAN FAMILIAL CASE OF BEHÇET DISEASE AFTER VARICELLA ZOSTER VIRUS INFECTION
Gerardi M.C.*, Batticciotto A., Talotta R., Ditto M.C.*, Atzeni F., Sarzi-Puttini P., ASST Fatebenefratelli L. Sacco University Hospital, Rheumatology Unit, Internal Medicine Department, Milan, Italy
Behçet’s disease (BD) is a multisystem vasculitic syndrome that is characterized by recurrent oral and genital ulcerations, ocular manifestations and additional clinical manifestations in multiple organ systems. The etiology of BD is unknown, yet to TA, while the etiologic factors contribute to the development of the disease. A genetic contribution to BD etiology has been suspected for several years on the basis of HLA association, a higher prevalence of BD in some ethnic groups, and the existence of familial cases. Although, the majority of patients with BD are sporadic cases with no family history, a familial aggregation of BD patients has long been noted mainly from Japan and Turkey. A possible role of viruses, particularly the Herpes group of viruses, has also been postulated. In this specific case we present an Italian family in which two of the family members, daughter and father, had BD. The proband, a 25-year-old woman, was admitted to the hospital complaining of recurrent fever and pain in genial aphtous ulcers. She was diagnosed three years prior to this with BD based on the clinical manifestations of recurrent oral and genial aphthous ulcers, and skin manifestations. On admission, the daughter had painful and multiple ulcerations of the oral mucosa and papulo-pustular lesions; the physical examination was otherwise unremarkable. Laboratory findings for complete blood cell count, ESR, CRP, blood biochemistry analysis and urinalysis were normal. Tests for ANA, anti ds-DNA, c-ANCA and p-ANCA were negative. HLA B51 antigen and the pathergy skin test were negative. The chest radiography and abdominal ultrasoundography were normal. Ophthalmological and neurological examinations were also normal. After unsuccessful treatment with colchicine, azathioprine, and methotrexate, in an attempt to reduce the dose of systemic corticosteroids, Adalimumab (40mg every other week) was administered and the clinical condition improved dramatically. The proband’s father, a 51-year-old man, was diagnosed with BD two years prior with oral and genial aphthous ulcers and skin manifestations. The HLA analysis revealed B51 antigen positivity. He was undergoing treatment with colchicine and intermittent prednisone. Both subjects were white Caucasians and Italians by descent. In both cases, the first symptom connected to BD was oral aphthous ulcer which had occurred after chickenpox. After 18 years from the oral aphthous onset, the daughter developed recurrent pain genial aphthous ulcers associated with fever and cutaneous papulo-pustular lesions. The father, after 19 years from the oral ulcers onset, developed recurrent genial aphthous ulcers and skin manifestations with papulo-pustular lesions. In both cases, laboratory test for varicella-zoster virus (VZV) revealed a VZV-IgG positivity and VZV-IgM negativity. To the best of our knowledge, this study provides the first report documentating familial distribution in Italian BD patients. Although the occurrence of BD in consanguineous subjects suggests a genetic etiology, the occurrence of the first symptom after a VZV infection may indicate a possible role of this virus in BD development.
Conclusions. The results of our investigation showed a high frequency of targeted SNPs in Italian patients. This finding supports the correlation between tagSNPs and BD previously reported in literature by several research groups for different populations. Our preliminary results need to be further confirmed in a larger cohort of patients and controls.

References

P38.

INVESTIGATING THE MUTATIONAL STATE OF ERAP1 GENE: THE IDENTIFICATION OF KNOWN AND NOVEL SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs) IN A COHORT OF ITALIAN BEHÇET’S DISEASE PATIENTS

Padula M.C.1, D’Angelo S.2, Amato G.C.1, Giusino R.1, Pellizzieri E.L., Gilio M.2, Leccese P.1, Olivieri I.2, Martelli G.1
1Department of Science, University of Basilicata, Potenza, Italy; 2Rheumatology Division, San Carlo Hospital, Potenza, Italy

Background and aim. Endoplasmic reticulum aminopeptidase 1 (ERAP1) is a key component of the pathway that processes the peptides to optimize their length for MHC-I binding. Single nucleotide polymorphisms (SNPs) in this enzyme have been associated with the susceptibility to several diseases, including Behçet’s disease (BD) (1-6). We aim to perform a replication study for ERAP1 tagSNPs rs2287987 (p.Met549Val), rs30187 (p.Lys528Arg), rs7148207 (p.Arg722Gln) and rs27044 (p.Arg730Glu) previously reported in Turkish (5) and Spanish (6) populations in a Southern Italian cohort. Additionally, in order to discover new BD-susceptibility markers, we also intend to genotype all ERAP1 exons and exon-intron boundaries.

Methods. We studied a total of 50 BD patients (mean age: 45.5 years; range: 26-67 years; sex ratio: 30M/20F). Genomic DNA was isolated from patient whole blood by means of standard procedures. A preliminary bioinformatic step of primer design, based on gene Reference Sequence (NG_027839.1), was performed by using NCBI Primer-Blast tool. In vitro PCR amplification and direct sequencing were carried out for molecularly studying ERAP1 whole structure. Downstream in silico analysis was also conducted for DNA variant analysis, PolyPhen-2 tool was also queried for predicting SNP functional effects.

Results. About known tagSNPs detection, rs2287987 was found in 13/50 patients (26% of cases); rs30187 in 29/50 patients (58%); rs7148207 and rs27044 respectively in 19/50 patients (38%) and 32/50 patients (64%). In addition, seven novel variations were found within ERAP1 exons. Two de novo SNPs resided within ERAP1 exon 2, rather than p.Arg539Pro and p.Glu56Leu: the first SNP was predicted to be damaging (maximum pathogenicity PolyPhen-2 score) and was found in 9/50 patients (18%). No pathogenic effect was recognized for the second change (p.Glu56Leu), whose frequency was equal to 26% of cases. Exon 3 p.Glu183Val and p.Phe199Ser were identified respectively in 85/50 patients (16%) and in 3/50 patients (6%); both showed a predicted pathogenic effect. Exon 4 p.Lys259Leu was a benign SNP with low frequency (3/50 patients, 6% of patients). The variation p.Glu337Gln of exon 6 was found in 5/50 patients (10% of cases); no functional impact was predicted for this change. The last SNP was located within the exon 7 of 650 patients (12%) and showed high predicted pathogenicity.

Conclusions. Here we reported known and novel ERAP1 variations in a cohort of Italian BD patients. Our preliminary data were consistent with an association between ERAP1 and BD. However, future genetic and functional studies, including a larger number of patients and controls, are required to validate our preliminary finding.

References

P39.

ELEVATED SERUM PROLACTIN IN EGYPTIAN PATIENTS WITH BEHÇET’S SYNDROME

Elsifawhi M.1, Elgeney F.1, Mossalamm G.2, Elifawshi S.2, Elifawshi M.1, Metwally I.1
1Kasr Alainy Hospital, Cairo University, Department of Rheumatology, Egypt; 2National Cancer Institute, Clinical pathology Department, Cairo University, Egypt

Background. Behçet’s syndrome is an autoimmune disease that is more prevalent among the countries of the ancient Silk Road. (1) Altered levels of prolactin in autoimmune diseases was reported but contradictory prolactin in Behçet’s syndrome and none was reported among Egyptian patients (2-3).

Objectives. The aim of the study was to investigate the prolactin level in a cohort of Egyptian patients with Behçet’s syndrome. Furthermore to associate the prolactin level with patient characteristics, genetic background and disease patterns.

Methods. Patients were enrolled from the Rheumatology department at Kasr Alainy Hospital. Patients fulfilled the International study group criteria for Behçet’s syndrome. Serum prolactin level was assayed for patients using electro-Chemiluminescence immunoassay. Normal References were obtained from a reference study validating the used immunoassay platform (4).

Results. Fifty-four patients were studied, among them (88%) were males the rest were females. The patients’ mean age was 35±24.985 years with mean disease duration of 9.3±3.7 years. The main clinical features were oral ulcers (100%), genital ulcers (100%), eye involvement (53.5%) neurological involvement (27.7%) and vascular involvement (37%). Erythema Nodosum was noted in 48% of the cons. Consanguinity was found in 22% of patients. HLA B51 was positive in 48%. Serum prolactin was significantly higher in the Behçet’s patients compared to normal reference (p-value=0.04). (mean serum prolactin was 10.9±6.86 ng/mL in patients compared to 8.86±2.87 ng/mL in normal reference). Serum prolactin was significantly lower in HLA B51 positive patients than in HLA B51 negative patients (p-value=0.033). Similarly consanguineous patients had statistically significant lower serum prolactin level (p-value=0.007). Patients with Erythema Nodosum had higher serum prolactin level however it did not achieve statistical significance (p-value=0.58). No other associations with disease presentation as ocular, vascular and neurological involvement were found.

Conclusions. Serum prolactin is elevated in Egyptian patients with Behçet’s syndrome. Genetic Backgrounds as HLA and consanguinity may affect serum prolactin in Behçet’s patients.

References

P40.

ALLERGIC REACTION TO ORAL BACTERIA IN PATIENTS WITH BEHÇET’S DISEASE AND THE RELATED DISEASES

Kaneo F.1, Togashi A.1, Nomura E.1, Nakamura K.1
1Southern TOHOKU Research Institute for Neuroscience, Institute of Dermato-Immunology and Allergy, Koriyama, Japan; 2Saitama Medical University, Saitama, Japan

Most of patients with Behçet’s disease (BD) tend to have hypersensitivity against streptococci (1) which might be acquired through the innate immune mechanism in the oral cavity, as previously described (2). Following recurrent aphthous stomatitis (RAS), BD patients generally have the systemic symptoms by immune reactions to streptococci and other related bacteria which are reported to be increased in number in the oral cavity (3). Then, we tried to prick with self-saliva to the forearm skin of the patients. It is of interest to find whether BD patients, non-BD patients with similar symptoms, herpes simlex virus (HSV) infection and healthy controls respond to streptococci included in self-saliva and whether the methodology could be used for a diagnosis of BD, although previously demonstrated about the reactivity in some studies in normal BD RAS (4).

Methods. The skin test was done on the forearm of the patients and controls using Lancetter (Sweden) with self-saliva, as follows, 1) Crude self-saliva (S), 2) sterilized salvia by syringe filter (SS), and 3) control saline (CS) were used and 4) pathergy test by 25G syringe needle was also done after surgical sterilized forearm skin of the patients and controls. The cutaneous reactions were observed 24-48 hours after prick.