Diagnosis, Misdiagnosis, and the help of classification/diagnosis criteria in Behcet’s Disease

Fereydoun Davatchi

Behcet’s Disease (BD), a multisystem vasculitis[1], is a rare disease seen essentially around the Silk Road[2]. The prevalence goes from 420 in 100,000 inhabitants in Turkey (the highest prevalence ever reported) to 80 in Iran, 14 in China, 13.4 in Japan, 8.6 in the US, 7.2 in France, and 4.2 in Germany. The lowest reported was 0.64 in the UK (Yorkshire County) [3-4]. As there are no specific laboratory tests for BD, and no imaging techniques, nor other paraclinical procedures, the diagnosis remains essentially clinical. It will depend highly on the experience of the physician. Therefore, Diagnosis/classification criteria may be of great help, especially for those with less experience in BD.

Although BD has aroused a large number of Diagnosis/classification criteria (17 up to now), the most used were the Japan criteria (1972), Dilsen (1986), and the International Study Group criteria (1990) known as ISG criteria, which was created by a collaboration of 7 countries[5]. Due to the lack of sensitivity of ISG criteria, the International Criteria for Behcet’s Disease (ICBD) was created by the collaboration of 27 countries in 2006 and was revised in 2016.

Nutritional aspects of the mosaic of rheumatic autoimmune diseases

Shani Dahan, Yahel Segal and Yehuda Shoenfeld

The concept of the “mosaic of autoimmunity” was initially coined in 1989 by Shoenfeld et al, referring to the complex interaction of genetic, hormonal, immunological and environmental factors in the pathogenesis of autoimmune diseases.

During the past decades, the incidence of autoimmune diseases has increased, whereas human genetics have not experienced much turmoil. In an attempt to elucidate this epidemiology, many environmental factors have been explored in relation to their correlation with autoimmune diseases. A prominent example is vitamin D deficiency, which has long been studied as one of the environmental factors in the development of autoimmune diseases such as multiple sclerosis (MS), type 1 diabetes and systemic lupus erythematosus (SLE).

Dietary habits have long been known to have a crucial influence on human health, affecting the risk for hypertension, heart diseases and stroke, as well as influencing the development of cancer. Therefore, when considering the complex web of factors compilling the mosaic of autoimmunity, it is not surprising that various novel dietary elements were recently found to play a role in disease development and prevention. In fact, there is no question that we are what we eat, and it is probably safe to assume every ingredient we

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Nobel prizes reflect the ultimate recognition of the highest quality human endeavor that impacts the world positively, isn't it? Ironically, Alfred Nobel's invention and manufacture of the dynamite intended to blast rocks was misused in destructive wars. I learnt that at school. Later when at the medical school I gathered that in 1901 the very first Nobel in Medicine and Physiology was awarded to inventors von Röntgen for X-rays (shared with von Behring for serum therapy to conquer diphtheria and tetanus). Providentially the first X-ray picture captured was of the hand of Mrs. Röntgen, totally unplanned. By the way, she was a victim of rheumatoid arthritis, have a look. Notice the reduction of joint space at PIP joints, the wedding ring besides. What a blessing in disguise. Europe commemorated this landmark invention by releasing a stamp a century later.

This year (2017-18), the Nobel was shared by three distinguished Americans ... for their discoveries of molecular mechanisms controlling the Circadian rhythm ... or stated simply Biological Clocks.

TIME is probably another invisible God demanding that everything must run on time, from time to time, even if times change calling for timely action to ensure clock-like precision to ensure human machinery follows circadium rhythms within adapting to environmental variables. At times it takes a little time; a down to earth example is the inevitable jetlag as we fly across time zones.

What actually is the Biological Clock, then? A central pacemaker is the Hypothalamic Suprachiasmatic Nucleus(SCN). It receives light inputs via retinohypothalamic tract. SCN synchronizes peripheral multitude minute clocks located within organs, the tissues and cells. This SCN and such minute secondary clocks are self-sustaining and are entrained by external cues eg. temperature and feeding arrangements among others.

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Central to this loop are the genes that regulate proteins: CLOCK / BMAL1 transcripting PER / CRY dimeric complex. Rheumatoid Arthritis is a good model of Circadian rhythm aberrations allowing therapeutic corrections:

It’s 77 years since Nobel was awarded in 1950 to Hench, Kendall and Reichstein for their landmark studies in rheumatoid arthritis patients experiencing remissions and exacerbations. Isn’t it high time that rheumatologists of today master the art of prescribing glucocorticoids to enhance benefit-risk ratio? Can we practicing rheumatologists bring justice to the three great Nobels won deeply connected to rheumatoid arthritis?


Flower Clock: Butchart Gardens
Victoria BC, Canada

Prakash Pispati  E-inC  VOA
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Master, Honorary Member and Past President – Asia Pacific League of Associations for Rheumatology
Director of Rheumatology, Mentor - Jaslok Hospital & Research Centre, Mumbai, India
Sr. Consultant Rheumatologist - Saifee Hospital, Mumbai, India
Past President –Indian Rheumatology Association

Recommended reading

The role of the circadian clock in rheumatoid arthritis

The Spirit of APLAR: Welcoming Poem

Kuala Lumpur greets u ...
And we welcome u ...
We open our hearts and open our souls ...
Kuala Lumpur sees the light ...
Kuala Lumpur turned bright ...
When U came along ...
When U came along ...
We greet u all and we welcome u ...
We open our hearts and open our souls ...
We see the light. Oh its so bright ...
Joy to our hearts ...
Joy to our souls ...
We welcome all of you... SELAMAT DATANG

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Idiopathic inflammatory myopathies (IIM) are heterogeneous disorders characterized by muscle weakness and muscle inflammation. The most common subgroups in adults are dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM), and in children, juvenile DM (JDM). A wide variety of diagnostic or classification criteria for myositis are used but are generally derived empirically and not validated. The criteria of Bohan and Peter are most widely used, but have limitations. So recently, the new criteria of IIM studied by IMCCP was released online at Sep. 2017.

The International Myositis Classification Criteria Project (IMCCP), an international collaboration with experts from adult and pediatric rheumatology, neurology, dermatology, epidemiology, and biostatistics was established in 2004 and followed the EULAR and ACR recommendations for development of classification criteria from that time or published soon thereafter. A steering committee and a larger working committee with experts in IIM were formed. Experts using the nominal group technique designed the study and validation experiments, assembled and defined candidate criteria from published myositis criteria and other characteristics of myositis, determined and assembled the IIM subgroup diagnoses and comparator conditions that were studied. Ninety three variables were selected by the steering committee for study in cases and comparators. A glossary and definitions were developed according to an ACR glossary. Data were abstracted from patients’ records and entered into a web-based database.

Cut-points for classification of IIM was in follow: The best balance between sensitivity and specificity was found for a probability of 55-60% for the criteria not including muscle biopsy data, and 55-75% when including muscle biopsies, or a total aggregate score of score of ≥5.5 and ≤5.7 (≥6.7 and ≤7.6 if biopsy is available). The IMCCP proposes that a patient may be classified as IIM if the probability exceeds a predetermined cutoff of at least 55%(corresponding to a score of ≥5.5, or ≥ 6.7 if biopsies are included) based on maximization of statistical performance and best balance between sensitivity and specificity. The level of probability ≥55% and <90% was defined as “probable IIM”. The Steering committee recommends, based on expert opinion, that “definite IIM” should equal a probability of ≥90% corresponding to having total aggregate score of ≥7.5 without muscle biopsy and ≥8.7 with muscle biopsy. Patients falling in the probability range of ≥50% and <55% will be classified as “possible IIM”. For a patient to be classified as a non-IIM patient the probability would have to be <50%(score of maximum 5.3 without biopsies; 6.5 with biopsies).

The new EULAR/ACR classification criteria provide a score with a corresponding probability of having IIM. This provides investigators flexibility in inclusion criteria for different types of studies, e.g. clinical trials requiring high specificity would warrant a high probability of IIM in the inclusion criteria, whereas epidemiological studies requiring high sensitivity would need inclusion criteria with lower probability or IIM. Compared to most previous criteria, the new criteria are superior in sensitivity, specificity and classification accuracy.

However, there are limitations of this new criteria:

1. no controls or comparators were included in the external validation cohort, since the IMCCP study was designed before those recommendations from ACR/EULAR were in place, requiring future validation.

2. Another limitation largely unavoidable in observational data is the high frequency of missing data in the derivation dataset and validation samples, reflecting differences in practice patterns in evaluating patients. Nevertheless, 80% of cases and comparators had muscle biopsy data available, whereas magnetic resonance imaging data and electromyography were only available for 38% and 29% of cases respectively, reflecting their limited usage in clinical. However, magnetic resonance imaging data and electromyography examination are still important for diagnostic purposes of IIM. Patients studied had to have their disease for at least 6 months, which did not allow us to study new-onset patients. Importantly, these criteria

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consume has some effect on our health and specifically on our immune system.

We chose to address several components of our diet for which there are relevant evidence as to their effect on rheumatic autoimmune diseases. First, salt was demonstrated to influence Th17 cells, which are known to play an integral part in several autoimmune diseases such as RA, SLE, MS and psoriasis. When examining the effect of high-salt diet on mice with Experimental Autoimmune Encephalitis (EAE), a murine model for MS, studies found the disease to be aggravated by high salt intake [18, 19], through different molecular mechanisms. A recent observational study performed in Sweden, evaluating 1285 subjects from the Epidemiological Investigation of Rheumatoid Arthritis (EIRA), showed an increased risk of Anti Citrullinated Peptide Antibodies (ACPA) positivity among high sodium intake heavy smokers. This eludes to a synergistic detrimental effect of sodium consumption and smoking in RA.

The next nutritional factor comprising the mosaic is the spicy food. Spices have been a cardinal part of culinary cultures around the world, with chili peppers being the most widely used seasoning, especially in China, Mexico and Italy. The beneficial effects of spices are related to their bioactive ingredients such as capsaicin. Capsaicin, the main active ingredient of chili peppers, is a phytochemical which is responsible for the characteristic hot taste of these plants. Recent studies have focused on investigating the influence of capsaicin in the pathogenesis of some autoimmune rheumatic diseases, with the most extensive data available in RA. Capsaicin was demonstrated to exert a beneficial effect in a clinical randomized controlled trial involving 31 RA patients. Topical capsaicin administration (0.025%), applied on painful knees four times a day, for a period of four weeks, was demonstrated to induce a 57% reduction in pain assessment as compared to the placebo group. Topical capsaicin has been also evaluated in severely affected fibromyalgia patients, demonstrating short term efficacy. In a randomized trial of 130 fibromyalgia patients, topical administration on 0.075% topical capsaicin 3 times daily for 6 weeks, resulted in a significant improvement of several pain outcomes, such as myalgic score and the pressure pain threshold, compared to controls.

Last but not least in the nutritional factors of the mosaic is Curcumin. Curcumin is a principal active component of the common spice turmeric, and its use dates back nearly 4000 years to India, where it has been used as a culinary spice and had religious significance. Recently, the scientific community began exploring this substance for its effects on the human immune system and immune pathologies. The described mechanisms for the effect induced by curcumin included elevated expression of anti-oxidative stress and anti-inflammatory related genes; increased Treg cells expression along with decreased Th1 expression; and a shift toward regulatory B cells, with a rise in protective anti-inflammatory antibody production [21].

A clinical trial that assessed the effect of turmeric supplementation on lupus nephritis patients, showed a significant decrease in proteinuria, systolic blood pressure and hematuria in the turmeric group, while the control group presented no significant effect. Peppers, is a phytochemical  which is responsible for the characteristic hot taste of these plants. To summarize, the mosaic of autoimmunity has been a well-established concept for more than two decades; however various pieces of the mosaic continue to unravel as research progresses. Autoimmune rheumatic diseases are chronic diseases, greatly influenced by the life style of their carrier. In light of this, nutritional agents represent an attractive alternative to...
conventional therapeutics and require further investigation.

Current data suggests dietary factors hold significant effects on both the innate and the adaptive immune system. While salt appears to promote inflammation in various mechanisms, it seems that consumption of curcumin and spicy food may attenuate immune hyperactivity. These factors compile a novel, unexplored mosaic of autoimmunity, leaving some piquant taste for more.

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**Select reading**
For ISG criteria, the presence of oral aphthosis is mandatory. Then if two of the following manifestations were present, the patient was considered to have BD: genital aphthosis, skin manifestations (pseudo-folliculitis, erythema nodosum), ophthalmic manifestations (anterior uveitis, posterior uveitis, retinal vasculitis), and positive Pathergy test.

In ICBD, a point system is used: Oral aphthosis gets 2 points, genital aphthosis 2, ocular manifestations 2, joint manifestations 1, vascular manifestations (arterial thrombosis or aneurysm, and venous thrombosis) 1, neurological manifestations (Central or Peripheral) 1, and positive Pathergy test 1 point. To be considered as having BD, the patient needs to get 4 points.

Another cause of misdiagnosis, especially by non-experts, is the misinterpretation of oral aphthosis, which may become frequent by non-experts. To avoid misdiagnosis, it is customary to say that when a patient fulfill the criteria, the diagnosis can be made if no other disease can explain the symptoms. A good example of criteria misdiagnosis may be a traumatic uveitis in a person with recurrent aphthous stomatitis (RAS)[8].

The low sensitivity of ISG criteria was shown by several studies from different countries5. The ICBD criteria were validated in Iran, Germany, and China. The revised ICBD was validated in Iran[7] and in Italy. Comparison of ISG versus ICBD original and ICBD revised criteria, in different cohort of patients (BD versus Control patients) shows the following results. These cohorts were: India (50 BD), Singapore (37 BD), the cohort of International patients for the creation of ICBD (2556 BD/ 1163 controls), Germany (86 BD, 38 controls), China (322 BD, 118 controls), Iran 2010 (6128 BD, 3400 controls), and Iran 2013 (7011 BD, 5226 controls).

The diagnosis may become easier, by using a good classification/Diagnosis criteria, especially for a non-expert. Unfortunately, in Behcet's Disease, some of the clinical manifestations of the criteria, are also seen frequently in the normal population (oral aphthous ulcers), or may be seen in other diseases too (erythema nodosum, ocular manifestations). Therefore, diagnostic errors may become frequent by non-experts. In such a case, it is advisable to have the patient fulfill the criteria, and make the diagnosis if no other disease can explain the symptoms. A good example of criteria misdiagnosis may be a traumatic uveitis in a person with recurrent aphthous stomatitis (RAS)[8].

The elementary lesion is a well-defined and distinct lesion.
painful round or oval ulceration. It has a white to yellowish necrotic base, surrounded by a red areola[3]. The number of aphthous lesions varies from one attack to another. Sometimes it is isolated, but most of the times two or more lesions are seen together. The diameter of lesions varies from one attack to another, from 1 to 20 mm, with a tendency to decrease under the treatment. The lesions heal spontaneously in 1 or 2 weeks, without treatment, but they have a high tendency to recur. The interval between recurrences also varies from one attack to another, from a few days to several months, or even more. Oral aphthosis is not specific to BD and can be seen in other diseases like AIDS, ulcerative colitis, Crohn disease, systemic lupus erythematosus, and so on. It is seen in 25% of the healthy population. There is no difference in the characteristics of oral aphthosis (OA) seen in BD patients and in the normal population[9].

The most frequent errors that we see in our Behcet’s Disease Unit are:
Pemphigus vulgaris, Lichen planus, Herpes simplex, Crohn’s Disease, Ulcerative Colitis, Drug Induced Neutropenia

Genital aphthous ulcers: The elementary lesion resembles oral aphthosis, except that lesions are usually larger, heal slower, and recur less frequently. In females, they are often larger than 10 mm, and deeper than oral aphthous lesions. They last longer, and produce Sequelae more frequently[3,9].

The differential diagnosis is mostly with pemphigus, lichen planus, and herpes simplex.

Therefore, to avoid errors and subsequent misdiagnosis, a Dermatologist must see the oral or the

(..... continued on Page 9)
genital ulcer to see if it is an aphthous ulcer or not.

It is important to remember that not every oral or genital ulcer is an aphthous ulcer. Only an aphthous ulcer can be used as a diagnostic criterion. In case of doubtful lesions, Dermatology consults is advised.

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APLAR Master Award

Select reading

Tailpiece...

Behcet's Disease?? Real Life Challenge

Acknowledged worldwide authority on Behcet's Disease, Professor Fereydoun Davatchi was honoured as Master of APLAR at APLAR Congress, Chennai, India, 2015.

Behcet's Disease is rare in India. When President of APLAR about 15 years back, I had the great privilege to visit his famous Department in Tehran. On the very last Sunday morning before departing for the airport I attended his usual clinic (Sunday a working day there). In those three hours some 50 patients which came in, I got to examine 26 patients of Behcet's Disease! ... unforgettable.

Last year at my clinic a glamorous professional singer at Bollywood came seeking advice on recurrent aphthous ulcers in the mouth. She was anxious, concerned as she could not sing lucidly at concerts. There were no systemic features at all but her ANA was repeatedly positive at 1 in 1280.

Every conceivable treatment prescribed by other multi-specialists had failed. She was receiving 40 mg. of oral steroids with which the aphthous ulcers would shrink only to reappear, with consequent side-effects of steroids. I prescribed pulse i.v. methylprednisolone with salutary result, though the aphthous ulcers reappeared after a few weeks. On serious reflection I ruled out prescribing B-cell depleting rituximab as she had absolutely no systemic features.

And now she has suddenly developed severe unilateral deafness in one ear and partial deafness in the other. All investigations other than audiometry contributed to a big Zero. Also various hearing aids with variable results were adding to her distress (“at times it produces a sonic boom as I yearn to listen to musical notes”). I tried to console and encourage her by citing the case of Beethoven. Modestly she responded “No comparison please, he was a class apart ... besides he was composing not singing. Thanks anyway Doctor”.

She deftly strives to sing at concerts by her 'inner voice'. Understandably, she doesn't think highly of doctors.

Esteemed Colleagues, any clues?

...Prakash Pispati  E-in-C - VOA
are proposed as classification criteria in research and in clinical trials, not as diagnostic criteria.

It took almost 10 years to assemble sufficient numbers of patients with these rare diseases and three subgroups did not have enough subjects to study adequately. During this period a new IIM subgroup became recognized, IMNM, of which only a few cases were included into the study. IMNM cases could thus not be distinguished from PM in the sub-classification tree. Another subgroup with few cases was juvenile PM, making a data-derived distinction from JDM impossible. However, pediatric rheumatology experts in the IMCCP recommended that the adult sub-classification of IIM could be used for juvenile PM by extrapolation. IBM cases were identified in the sub-classification tree by the clinical features of finger flexor weakness and no response to treatment, OR by the presence of rimmed vacuoles in muscle biopsies.

Another limitation was the low frequency of myositis-specific autoantibodies documented. Five myositis-specific autoantibodies were included: anti-Jo-1, anti-Mi-2, anti-SRP, anti-PL7 and anti-PL12 antibodies and all were strongly associated with IIM. However, only anti-Jo-1 autoantibody had a significant number of observations to permit analyses and inclusion in the classification criteria. A future update of the EULAR/ACR classification criteria should include the more recently-identified myositis-specific autoantibodies, in addition to more patients with IMNM, ADM, hypomyopathic DM and juvenile cases other than JDM.

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Recommended reading

Laugh it off Doc...

Long term NSAIDS

Long term Steroids

Short term induction

Thanks to Dr. Subramanian Nallasivan, Yuva Vishalini Ravindran, Intern, Velammal, Harish, Intern, Velammal, India
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Abstract Submission Deadline  Tuesday, June 5, 2018
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Preliminary Program

IMMUNE-MEDIATED DISEASES
1. General
   - Biosimilars: Are rheumatologists and patients ready for transitioning
     patients from an originator to a biosimilar?
   - How to deal with vaccination of patients with inflammatory arthritis.
   - How to best manage osteoporosis in patients with arthritis.
2. Rheumatoid Arthritis
   - After cancer, which biologic should you use?
   - JAK inhibitors should be first line before biologic agents.
   - Pregnancy, biologics, and targeted synthetic disease-modifying
     antirheumatic drugs.
   - When is biologic monotherapy the treatment of choice?
3. Spondylarthropathies
   - Non-radiographic spondylarthropathy: If you were paying for it, would you
     commence biologic therapy?
   - Psoriatic arthritis: How to balance management of the skin and the joints.

LUPUS, VASCULITIS
- Lupus and pregnancy: Good news for the doctor and the mother.

OSTEOARTHRITIS
- Inflammation in osteoarthritis as therapeutic target.
- SYJSOA: Effectiveness in treating OA symptoms and maybe more.
- Intra-articular therapy for osteoarthritis: Interesting new findings for patients.
- Management of challenging osteoarthritis cases in daily practice: Well kept
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- Stem cells and other cellular therapies for osteoarthritis.

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