The majority of autoimmune diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), are multi-factorial diseases that develop through the interaction of several factors, such as genetic and environmental factors. A limited number of disease susceptibility genes such as those of the major histocompatibility complex have been known to exist for several decades. After these eras, genome-wide association studies (GWAS) have identified a large number of loci that contribute to the risk of autoimmune diseases. These findings have led to a better understanding of the genetic basis of autoimmune diseases and have opened up new avenues for the development of targeted therapies.

Raynaud's phenomenon (RP) is one of the common symptoms encountered in Rheumatology practice. The biggest challenge for a clinician is to differentiate between the primary and the secondary RP. There are a few clinical clues and investigations that may help a Rheumatologist to differentiate between the two as depicted in Table 1.

Out of all these features, Nailfold capillaroscopy (NFC) has an exceptionally high negative predictive value for primary RP. NFC is a non-invasive, bedside tool that can be easily performed in the office setting. It involves the examination of the capillary network in the nailfold, which can reveal characteristic changes such as dilated capillaries, capillary dropout, and Tortuosity.

Table 1 - Differentiating features primary vs secondary Raynad's phenomenon

<table>
<thead>
<tr>
<th>Feature</th>
<th>Primary RP</th>
<th>Secondary RP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>ANA positivity</td>
<td>Frequent</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Association with SCTD</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Complications</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Characteristic NFC changes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

(... continued on Page 4)
From the Editor’s Desk

LOndon …. right behind the Big Ben is this renowned historic Westminster Hospital. Rheumatologist Professor Derrick Brewerton was enjoying lunch and gossip with Dr. David James who had just returned from Africa (see below). Painstaking research followed unraveling the mysterious triangular affair between HLA B27, the sacroiliac joints vis-à-vis Ankylosing Spondylitis and ‘cousins’ the Spondarthropathies. May I present to you this fascinating story rather unusually. After all a picture is worth a thousand words, isn't it? The ‘mysterious triangle’ between HLA B27, Sacroiliac joints and Ankylosing Spondylitis can be as intriguing as the ‘Bermuda triangle’. When at a short sabbatical at Oxford some 15 years back, I was a witness to a brainstorming session between rheumatologists and geneticists. Two of them had returned from Africa wondering why AS is a rare disease there. They postulated that subsets of HLA B27 gene presented

(... continued on Page 3 )
clues eg. probably 2705 makes Caucasians vulnerable and 2701 makes Africans resistant to AS.... Since then we know a lot, time is not away when genetic manipulation may make human species less vulnerable to AS.

As a medical student we were taught four cardinal principles were paramount while examining a patient:

Inspection, Palpation, Percussion, Auscultation. Try it on SI joints in a patient with low back pain. You will be foxted because SI joints cannot be seen, touched or heard .... only indirect tests clinical, laboratory and imaging to assist never foolproof.

The tiny pair of SI joints, what are they actually, structurally? ; Synovial, cartilaginous or fibrous? This question I often pose to medical audiences, rarely to get a right answer. Gray's Anatomy in minute detail will tell you that SI joints are synovial for a start, turning cartilaginous after 35 – 40 years of age wisely permitting lumbotomy position during parturition in women, then over time turning fibrous. Check it out !The deep-seated pair of SI joints are hard to reach by invading microorganisms directly sometimes via blood stream but mostly by remotely controlled cytokines triggered by abnormal microbial flora in the gut, the larynx, the skin, the lungs, the urinary / the reproductive tracts ... We blame such diverse microbes as Gram negative, Gram positive, acid fast microorganisms, viruses, even parasites ! So we have different subsets under one generic term Reactive Arthritis.

Strangely, commonly used tests such as Rheumatoid Factor, Anti-CCP, ANA and subsets, ANCA, APLAs etc. are strictly all negative. So the definition Seronegative Spondyloarthritis. As new biomarkers are discovered / invented, the prefix Seronegative may become minimal or cancelled out.

Indeed I find this ‘love triangle’ between HLA B27, SI joints and Ankylosing Spondylitis mysterious. No wonder the theme alongside complex collagen vascular diseases dominates most Rheumatology congresses.

National Geographic to mark 150th Birth Anniversary of Charles Darwin had a specially designed cover page. Inside, It predicted that gene - environment interaction can be modulated to predict, prevent diseases protecting us hopefully. Is this happening? Pose this question to the new breed of genetic bioengineers.... the future is upon us. Till then, am afraid we have got to bear the burden of backache probing its backyard.

Prakash Pispati, M.D., F.R.S.M. (Lon.), M.Sc (Med.), FICP
Editor-in-Chief : Voice of APLAR
Master – American College of Rheumatology
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

Snippet...

60,000 kg

11,000 kg

914 kg

65 kg

Are quadrupeds adept at weight bearing? Are we bipeds poor in our backs?

Count Leo Tolstoy seemed bothered likewise so he guessed, “Man is the only animal that walks on two legs, drinks when not thirsty and makes love in all four seasons.”

How true, isn’t the human zoo a biologist’s nightmare?

Prakash Pispati, E-in-C
These findings have contributed to our understanding of the pathogenesis of these diseases. As the analysis of susceptibility genes has progressed, it has become apparent that many disease susceptibility gene variants are involved at the expression level of genes, which is called expression Quantitative Trait Locus (eQTL). Furthermore, expression of genes related to disease pathogenesis is cell-specific, with involvement of epigenetic mechanisms. Genetic information exists before the onset of disease, and thus has a causal relationship to the disease. Therefore, the analysis of genomic function in human autoimmune research is essential, with regard to understanding the pathological mechanisms as well as having applications for drug discovery.

have been used for more than 10 years to identify susceptibility genes for several autoimmune diseases.

Can patients with ANCA associated vasculitis be treated with complement blockade?
A synopsis of invited talk in BMJD 2017 Annual Congress, Gold Coast, Australia, August 31st to September 3rd 2017

The histopathological hallmark of ANCA-associated vasculitis (AAV) is “pauci-immune” necrotizing crescentic glomerulonephritis, characterized on renal histology by little or no glomerular staining for immunoglobulins and complement. Therefore, it was previously assumed that the complement system is not involved in the pathogenesis of AAV. However, increasing evidence suggests that activation of the complement system, via the alternative pathway, might play a role in the development of AAV. In a mouse model of AAV induced by anti-MPO IgG, C5-/mice developed no disease, indicating complement activation is vital in the development of AAV. C4-/mice developed disease comparable with wild-type mice, indicating that neither the classic nor the lectin complement activation pathways are required for disease induction. In contrast, B-/mice developed disease, indicating that alternative pathway complement activation is required for induction of AAV.

Fig 1. Co-localization of complement components in glomeruli of MPO-ANCA positive patients with microscopic polyangiitis (MPA) using direct immunofluorescence assay on frozen renal biopsy tissue. The colocalization of C3d and the complement activation end product membrane attacking complex (MAC) indicated that complement was activated in ANCA associated vasculitis; Colocalization of factor B (FB) and MAC indicated that alternative pathway was involved, while no colocalization of C4d and MAC indicated that neither the classical pathway nor the lectin pathway were involved in ANCA disease.


Fig 2. Evidence from circulation, kidney tissue and urine demonstrated that complement activation via alternative pathway in ANCA disease. The interaction between complement activation product C5a and its receptor C5aR may play an important role in the pathogenesis of ANCA disease.

(... continued on Page 5...
Fig 3. The three pathways of complement activation: the classical, mannose-binding lectin and alternative pathways. Three pathways of complement activation exist: the classical, mannose-binding lectin (MBL) and alternative complement pathways. Activation of the classical pathway begins with the binding of immune complexes to C1q followed by the activation of its C1r and C1s serine protease subunits. Then, C1s activates C4 and C2, which subsequently results in the formation of the classical pathway C3 convertase, C4bC2a. The alternative pathway is initiated by the hydrolysis of C3. Factor D cleaves the C3b-bound factor B, resulting in the formation of C3bBb, the C3 convertase. The lectin pathway is activated through the binding of MBL and mannose-associated serine protease 1 (MASP). MASP can cleave and activate C4 and C2 to form C4bC2a. Activation of any abovementioned pathway leads to activation of C3. Activation of C3 generates C3b and C3a, a chemo-attractant factor. Sufficient activation of C3 leads to the activation of C5. C5 activation leads to the formation of C5a and C5b-9.


Fig 4. Proposed working model for the interaction of anti-neutrophil cytoplasmic antibody (ANCA), neutrophils and complement activation in the pathogenesis of ANCA-associated vasculitis. Neutrophils are primed by cytokines, such as C5a or TNF, which leads to the translocation of ANCA antigens from cytoplasm to the cell surface. ANCA can further activate primed neutrophils to undergo a respiratory burst and degranulation, and release tissue factor (TF) bearing microparticles and NETs. Activated neutrophils can lead to the injury of endothelial cells, activation of the coagulation system, and activation of the alternative complement pathway via their cell membranes, microparticles and NETs. Activation of the alternative complement pathway and NETs in turn leads to the generation of C5a, which amplifies the inflammatory response through enhanced neutrophil recruitment and priming of neutrophils for ANCA-mediated activation.

In human studies, we found that vasculitic lesions in affected glomeruli stained for complement factors C3d, Bb and C5b-9; our further studies identified that levels of the unique alternative complement pathway factor Bb, measured in serum, urine and renal histology, closely associated with disease activity.

Recent studies indicated that the interaction between C5a and C5a receptor (C5aR) on neutrophils composes an amplification loop and thus, plays a central role in the pathogenesis of AAV. In human studies, circulating level of C5a in active AAV was significantly higher, compared with AAV in remission. In vitro studies indicated that C5a could dose-dependently prime neutrophils for ANCA-induced respiratory burst and degranulation. The generation of C5a could also lead to infiltration and degranulation of more neutrophils at sites of complement activation resulting in the development of inflammation.

Targeting the complement system is emerging as a novel treatment approach for AAV. Eculizumab, a humanized recombinant monoclonal antibody against C5, was used in an AAV patient with success. The recently released CLEAR study, a multicenter phase II randomized double-blinded placebo-controlled trial led by EUVAS, demonstrated the efficacy and safety of CCX168 (avacopan), a small molecule inhibitor of C5aR, in patients with AAV. This study showed that CCX168 could replace corticosteroid treatment with a more rapid onset of effect and lower adverse effects. A parallel phase II study of CCX168 on AAV conducted in North America, CLASSIC, showed similar results.

In conclusion, activation of the complement system via the alternative pathway plays a major role in the pathogenesis of AAV. Blocking complement activation, especially inhibition of C5aR might be a promising therapeutic option for patients with AAV.

Ming-Hui Zhao, MD, PhD
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Beijing 100034, PR China

...continued from Page 1 ...Nailfold Capillaroscopy

...predictive value and good positive predictive value for early distinction between primary and secondary RP. Sadly, NFC remains a grossly underutilized investigation despite its proven role in Rheumatology practice. Presently, the gold standard tool for NFC is a nail fold video capillaroscope (NVC). NVC is an expensive equipment with limited availability in developing countries. Despite the obvious advantages and the undisputed diagnostic value, NFC using NVC largely remains underutilized, mainly due to cost factors, lack of expertise and availability issues. The silver lining is that several other instruments such as Ophthalmoscope, dermatoscope, USB microscope and stereomicroscope can also be effectively used for NFC albeit with few limitations.

IMPORTANCE OF NFC IN RHEUMATOLOGY

The consensus emphasizes that all patient with RP should undergo a NFC examination to assist in characterizing the clinical and evolving profile. Besides, there is a myriad of information that can be obtained by NFC in various Systemic connective tissue disorders (SCTD) and other systemic diseases with microangiopathy, such as Coronary artery disease and Diabetes Mellitus. One of the best advantages for clinicians can have with NFC is its high negative predictive value for CTD (>90%) in subjects with RP. On the other hand, its positive predictive value is only about 50% but this is higher than any other single screening test including autoantibodies. NFC changes have also been included as a part of the recently updated classification criterion for systemic sclerosis by the European League Against Rheumatism (EULAR) in 2013. NFC changes can be very useful in differentiating Dermatomyositis (DM) and polymyositis (PM). In DM, there are florid NFC changes as against minimal changes in PM. Scleromyositis is an overlap syndrome combining features of SSC and DM/PM, associated with the positivity for anti-PM/Scl antibodies, more benign course than SSC, and normal capillaries on NFC. However, gross NFC abnormalities may predict emergence of typical SSC.

Antiphospholipid syndrome (APS) and small-vessel vasculitides can both present with NFC changes in form of multiple microhaemorrhages and hemosiderin deposits, with morphologically normal capillaries.

(..... continued on Page 7 )
INSTRUMENTS FOR NFC

NVC is considered the gold standard for carrying out NFC. The major drawbacks for use of NVC for NFC are its cost, time factor, need for special training and its non suitability for use in the OPD services. Various factors especially cost and specialized training is a major hurdle in popularizing this extremely important investigation.

We recommend simple, inexpensive instruments like USB microscope, Capillaroscope and handheld microscope for clinicians in OPD practice. However, NVC is ideally suited for research activities as well as analyzing subtle abnormalities and complex calculation of various indices. The major advantages and disadvantages of each technique are summarized in Table 2.

METHODOLOGY

However, for screening purposes in a busy OPD, examination of ring and little finger is enough. We analyse the stored images for linear capillary density, capillary tortuosity, variability in capillary length, number of enlarged capillaries, avascular areas and presence of disorganized architecture. We classify the observed changes in NFC as normal, scleroderma pattern or non specific abnormalities.

'Scleroderma pattern' is characterized by the presence of dilated capillaries.

Fig 2. Characteristic nailfold capillaroscopy findings in subjects using USB digital microscope A & B- Normal NFC at 30 X and 100 X, respectively. C - Dilated capillary loops with reduced capillary density in systemic sclerosis. D - Non specific dilatation and tortuosity in SLE. E - Completely disorganized architecture in advanced systemic sclerosis. F - Measurement of capillary density by photographing millimetre scale alongwith capillaries.

(..... continued on Page 8 )
Can you treat systemic lupus erythematosus when you can't see or recognize a target?

Tommy Cheung

Treatment to target strategy has proven very effective in may chronic diseases eg RA. Therefore it is reasonable to consider this treatment approach in SLE. Treatment of SLE should aim at ensuring long-term survival, preventing organ damage and optimising health-related quality of life, by controlling disease activity, minimising comorbidities and drug toxicity. The treatment target of SLE should be remission of systemic symptoms and organ manifestations.

Clinicians should continue to treat and monitor patients with SLE aggressively. Patients with renal lupus, treat to target strategy should be implemented according to the Joint EULAR/ERA-EDTA recommendations for the management of lupus nephritis. Complete renal response should be the ultimate therapeutic goal, which is defined as urine protein less than 0.5 gm per day and normalization of renal function.

In addition to tight control of disease activity, other strategies should be implemented to prevent disease flare as it is a major contributing factor for damage accrual. Use of immunosuppressive agents should be considered for all patients as it is effective in preventing major flares and reducing cardiovascular morbidity. Although serological activity is associated with the risk of disease flare, it is currently not recommended to intensify treatment in patients without clinical activity because the use of immunosuppressive agents, in particular glucocorticoid, can lead to further organ damage.

**CONCLUSION**

**Nailfold capillaroscopy (NFC) is a simple and non-invasive technique for the analysis of microvascular abnormalities seen in various SCTD, especially in SSc group of disorders.** NFC despite its immense potential remain grossly underutilized owing to certain shortcomings of “Gold standard” equipment. Our innovative, cost effective techniques for NFC using handheld microscope, USB digital microscope and capillaroscope are ideally suited for clinicians in a busy OPD practice. All this comes at a fraction of a price of NVC and ideal for resource poor countries. The only disadvantage is that it is less than ideal technique for modern research activities.

**APLAR Hon Treasurer Dr Debashish Danda installed President IRA 2017 -2019**

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...continued from page 7 ...Nailfold Capillaroscopy megacapillaries and decreased capillary density with vascular deletion areas. Non specific capillary loop abnormalities include mild capillary dilatation, variability of loop length and mildly reduced capillary density. Some of the images and typical abnormalities recorded with simple USB microscope are shown in Figure 2.

**CONCLUSION**

Nailfold capillaroscopy (NFC) is a simple and non-invasive technique for the analysis of microvascular abnormalities seen in various SCTD, especially in SSc group of disorders. NFC despite its immense potential remain grossly underutilized owing to certain shortcomings of “Gold standard”
Wonderful APLAR Congress - Dubai 2017

EXCERPTS FROM OFFICIAL REPORT FROM LEBANON

The scientific programme comprised of:
- 110 Faculty Members from 23 Different Countries
- 6 Plenary Lectures
- 32 Scientific Sessions
- 6 Special Sessions
- 12 Industry Sponsored Symposia
- 40 Oral abstract presentations
- 480 Poster presentations

VIEWPOINT OF A MEDICAL STUDENT:

The 19th edition of APLAR was held at the World Trade Center, Dubai. It kicked off on the 17th of October, 2017 with a Welcome and introductory speeches on the future aims and cares to be offered for rheumatology patients, both young and old, by Chairman Emirates Rheumatology Society, Dr. Waleed AlShehhi and APLAR President Dr. Kazuhiro Yamamoto at the glittering Congress inaugural.

The much awaited Great APLAR debate by Dr. Waleed AlSheehi and Dr. John Cush took place in the post lunch session of the last day. It started as a fun filled session as Dr. AlSheehi started the debate asking us to always remember the man in white and the man with the blue tie by which he projected himself as an equivalent to Mahatma Gandhi and his opponent to Donald Trump!

Dr Yuva from India presented a poster about lupus nephritis along with her guide Dr. Subramanian Nallasivan, and Dr Divya who presented posters about Biosimilars in rheumatology and Clinical profile in Pediatric rheumatology as well.

The grand finale was the closing ceremony marking the 1st anniversary of Voice of Aplar, replete with cake cutting by the Chairman Dr Waleed AlSheehi and President of APLAR Prof Yamamoto with all the esteemed Ex Com members on the stage... thanks to E-in-C of VOA Prakash Pispati, efficient APLAR and event managers.
PAKISTAN SOCIETY FOR RHEUMATOLOGY
22nd Annual International Conference
April 6th-8th, 2018
Pearl Continental Hotel, Lahore
Organized by
Division of Rheumatology
FMH College of Medicine and Dentistry

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F I R S T  A N N O U N C E M E N T

19th MSR-SSR Workshops in Rheumatology 2018
ROAD TO SUCCESS in RHEUMATOLOGY
3rd - 5th August 2018
One World Hotel Petaling Jaya, Selangor, Malaysia

Organized by:
A P L A R
Asia Pacific League of Associations for Rheumatology

Online information / registration:
http://msr-ssr2018.com
With the advent of newer technologies, Rheumatoid arthritis is being diagnosed earlier and earlier now. There is also the concept of Very Early Rheumatoid Arthritis. The ACR came around with the new criteria in 2010 precisely so that we could diagnose them early. The stakes are high with the availability of biologics, and now, small molecule therapy. These are costly drugs and it only makes economic sense to try and get our subjects of RA into remission, or possibly, cure, as early as possible to justify their use.

There are different definitions of remission ranging from clinical to ultrasound to molecular ones (1). The concept of molecular remission or low disease activity (equivalent to minimal residual disease) comes from our oncology colleagues. With treat to target strategies for RA and the routine use of outcome measures, it should only be a matter of time and picking up early disease that our subjects should all be in remission! But is it indeed so? What is happening in the real life world?

Remission in RA has been studied prospectively and otherwise and there is already published data to it. While most of it comes from the West (2), there is some from the Asian subcontinent also (3,4). At APLAR 2017 this year, in Dubai, we therefore got together to form a ‘Special Interest Group’ in RA and representatives from different countries from Asia participated in the meet to look into what we could achieve together. As a first, under the guidance of Prof Zhan-Guo Li we will be looking at the cross sectional data on what proportion of our real life OPD subjects of RA are in remission with details of what treatment they have been on and other variables. We plan to collate data from the different countries by the end of March 2018.

As the pressure for pushing our subjects earlier into remission mounts, and rightly so, we hope to capture what we are doing and as a follow up some time in a later study how to improve upon it so that together, as a fraternity, we are able to see our subjects free of their disease, on (remission) or, more optimistically, off (cure) drugs.

As we go about doing this, one is but reminded of the famous saying ‘No one can whistle a symphony, it takes a whole orchestra to play it’.

Sapan Pandya
Member SIG RA
Rheumatologist, Ahmedabad, India
Dear friends and colleagues,

Please come to Kaohsiung, Taiwan for the 20th APLAR Congress in 2018. We have prepared a rich program with exciting social events. Kaohsiung's sunshine and cuisine are just amazing. Make sure you will be there.