DISCLOSURES

- NONE -
RHEUMATOLOGY PERSPECTIVE ON PSO COMORBIDITIES

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The Fight for Dominance
COMORBIDITIES OF PSO

CLASSIC

Symptoms
- COLITIS
- UVEITIS
- ENTHESITIS
- DACTYLITIS
- SPONDYLITIS
- NAIL DYSTROPHY

WHAT ABOUT

Depression
- Stress / sleep / sex disorders

Hypertension

Diabetes
- Obesity

MACE
- MI / Stroke

Metabolic Syndrome
Sleep Disorders in PSO/PSA

Incidence of insomnia in PSO has been estimated from 5.9%–44.8% identified in 33 studies, where the general population is at 10% and up to 35% with transient insomnia.

HOWEVER, incidence of Obstructive Sleep Apnea is 36–81.8% compared to general population of 2-4%.

In a second study the incidence of insomnia in PSA was 84%, PSO 69% and controls 50%.

Gupta et al, DOI:10.1016/j.smy.2015.09.003. Wong et al, DOI: 10.3899/irheum.161330
IMMUNOLOGY OF SLEEP

Sleep Deficit Associated with:

- Increased TNF alpha
- IL-1B, IL-17, CRP, NO, adenosine, and PGS.

Impact on target organs:
- Impact on target organs: an increased level of HTN, CV complications, metabolic disorders and generalized performance impairments.

Ultimately, poor outcomes as cytokine upregulation is related to hyperesthesia, pain, fatigue and depression.

Sleep supports the immunoregulatory system

Sleep deprivation leads to a proinflammatory state

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Study of 62 PSA, 52 PSO patients, and control group,

Measures
DAS28, FACIT, HAQ, PASI, PSQI, VAS pain

Results
67.7% of PSA, 57.7% of PSO pts and 14.6% controls were found to have poor sleep quality.

This resulted in worse quality of life and intense fatigue. However, tx with TNF alpha inhibitors led to improvement of sleep quality.

FACTORS THAT APPEARED TO WORSEN SLEEP QUALITY

Factor 01
PSO; duration of dz, severity of skin lesions, Patients age

Factor 02
PSA; duration of PSO, TJC, CRP, pain , Pt’s age

Discomfort from psoriasis may interfere with sleep

Sleep deprivation may lead to increased stress

Stress may trigger PSO/PSA activation

**IMMUNE RESPONSE:** Elevation of IL6, MCP1, prostaglandins, There is dynamic change of microglial activation upregulated by IL-1

Cytokines down regulate cyp 450 system.

Up regulation:
- NFkB
- IL6, IL8, and type 1 IFN including innate activation of TNF alpha, IL1 b, TL R3, TLR 4, as well as CRP AND MCR4:

They maybe markers of depression and potential predictors of response

Polymorphisms (i.e., TPH2 GENE) have been identified in depression which may be the etiology of treatment failure

Schmidt, et al., Curr Neuropharmacol 2016
Miller et al., role of inflammation in depression: from evolutionary imperative to modern treatment target; 10.137/ doi 10 1038nri;2015.5, vol 16, jan 2016
PSO IMPACT ON DEPRESSIVE PHENOMENA

SYMPTOMS
Higher rates of depression have been noted in PSO/PSA
Higher risk of sexual dysfunction noted

RESEARCH
Meta analysis of 8 studies evaluating sexual dysfunction in 4039 pts from 1966-2011

RESULTS
48% reported diminished sexual function negatively affecting orgasm, ED, over all decline in function
Depression higher in this group
**PSO IMPACT ON DEPRESSIVE PHENOMENA**

**STUDY**
1 STUDY REPORTED: 9% PTS WERE SATISFIED WITH PROVIDERS ATTENTION TO THESE ISSUES
43% FELT PROVIDERS ATTENTION TO SEXUAL MATTERS INSUFFICIENT

**STUDY**
15 EPIDEMIOLOGIC STUDIES SHOWED PREVALENCE OF SEXUAL DYSFUNCTION RANGED BETWEEN 26%-71%.
CASE CONTROLLED TRIAL SHOWED 53.7% AFFECTED VS 17.5% CONTROLS

**RESULTS**
AND OF COURSE LOCATIONS OF THE LESIONS HAD SEVERE IMPACT ON SEXUAL DYSFUNCTION

Psoriasis Longitudinal Assessment and Registry (PSOLAR)

- 14.7% were depressed
- 11.1% were anxious
- 64.7% using alcohol
- 23% current smokers
- 32.9% prior use of tobacco

Patients with diminished HRQoL were less likely to adhere to TX
- 60% with severe PSO had increased lost days at work and decreased work productivity
- 87% of family members had decreased QOL.

PSO & METABOLIC SYNDROME

Prevalence of metabolic syndrome in PSO

- 140 patients with chronic plaque psoriasis/ 140 controls
- RESULTS: 39.3% with MetS VS 17.1% CONTROLS
- OR=3.13
- SIGNIFICANTLY HIGHER –HTN, ABDOMINAL OBESITY AND DM AND OSA (or=2.87 in @2500 pt meta-analysis)
- TRENDS: SIGNIFICANT INCREASE IN DM, HTN AND T2D WITH INCREASED SEVERITY AND DURATION OF PSO
- In a pooled meta-analysis-20 countries=1,450,188 total with 46,714 PSO pts-random effects analysis = OR of 2.14
PSO & HYPERTENSION

INCIDENCE

OF HTN IN PSO—24,285 PTS AGE MATCHED CONTROLS AND 12,502 PSO PTS

PREVALENCE

= 38.8% PSO VS 29.1% CONTROLS—p<.001

ANALYSIS

Multivariate analysis controlled for DM, SMOKING, AGE, GENDER, NSAIDs

IMMUNE REGULATION OF HYPERTENSION

CLASSICAL DEFINITION: "BP > 120/80"

ALTERNATIVE DEFINITION: "HYPERTENSION IS AN AUTOIMMUNE RESPONSE TO ALTERED SELF".

TH1, TH2, TH17, GAMMA INTERFERON, and FOX P3; up regulates ANGIOTENSIN-2 AND MINERALOCORTICOIDS.

Schiffin et al., dept of med, McGill Univ. Aug 17 2012
ISOKETAL ADDUCTS (GAMMA KETOALDEHYDES) ARE FOUND IN HIGH CONCENTRATION IN DENDRITIC CELLS IN PATIENTS WITH HTN.

1. OXIDATIVE MODIFICATION OF SELF PROTEINS

2. INCREASES IL6, IL1B, IL23, AND CO-STIMULATORY PROTEINS; CD80-86, CD8, IFN GAMMA, IL17A, AND PLASMA F2 ISOPROSTANES.

Schiffin et al., dept of med, McGill Univ. aug 17 2012
RHEUMATOLOGY PERSPECTIVE ON PSO COMORBIDITIES

OF CYTOKINE RELEASE IN HTN

Adaptive immune cells

CD8+ T cell

CD4+ T cell

γδ T cell

IFN-γ, TNF-α, Granzyme B, Perforin

IL-17A

IFN-γ

IL-17A

Hypertension

IgG

B cell

Treg

Innate immune cells

Macrophage/
 microglia

12/15 LO

Monocyte

NLRP3
inflammasome

IL-6, IL-1β, TNF-α

ROS, IL-1β, IL-18

NLRP3
inflammasome

ROS, isoLG, IL-6, IL-23, IL-1β, IL-18

The Journal of Experimental Medicine

immunology of hypertension | JEM
HX OF HYPERTENSION

IN 2007—HARRISON et al., looked at the role of T cells in HTN in RAG1 DEFICIENT mice.

ANGIOTENSIN 2/DOCA+NACL DID NOT INCREASE BP.

HOWEVER: SYNGENEIC T CELL TRANSFER ALLOWED MICE TO EXPERIENCE THE HTN.

DOCA=DEOXYCOTICOSTERONE ACETATE
RAG-1 DEFICIENT MICE = NO MATURE B/T CELLS
GWAS large overlap of genes that govern CAD and MetS

Severe Psoriasis is an independent risk factor for myocardial infarctions in younger patients. RR=1.29 for a 30 yr old with mild dz and 3.10 for severe dz.

Prognosis post MI in PSO patient is worse than general population

Duration of Disease is an independent risk factor for every additional yr of dz, there is a 1% increase in MACE

MACE increased over 3-5 yrs by 36% if PSA was present

ICAM, VCAM, E-SELECTIN (ELAM-1), MPO, TMAO

ADMA/SDMA IS INCREASED IN HTN, CKD, DM AND DYLIPEDEMA AS WELL AS SERVE AS A RISK FACTOR FOR CV DISEASE AND PLAQUE FORMATION

alpha MSH IMPROVES VESSEL RELAXATION VIA NITRIC OXIDE PATHWAYS

EF = ENDOTHELIAL FUNCTION – ADMA/SDMA = ASYMMETRIC/SYMMETRIC DIMETHYL ARGININE (METABOLIC BYPRODUCTS OF CONTINUED PROTEIN MODIFICATION IN HUMAN CYTOPLASM).
EF AND PSO

EVIDENCE FOR INCREASED HOMOCYSTEINE IN PSORIASIS
ELEVATED HOMOCYSTEINE LEADS TO ELEVATED ADMA
TNF alpha elevates ADMA and leads to reduction in NO

HAS BEEN STRONGLY ASSOCIATED WITH PASI SCORES
IS ASSOCIATED WITH EF
MAY PLAY A ROLE IN PATHOGENESIS OF PSO
ON THE HORIZON AS A MARKER OF DISEASE ACTIVITY

<table>
<thead>
<tr>
<th>37 PSO PATIENTS</th>
<th>LAD FLOW MEASURED BY DOPPLER ECHO</th>
<th>MEASURED AFTER 6.3 MOS OF ANTI TNF THERAPY</th>
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<td>AGE 31- NO CV DZ</td>
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FURTHER STUDIES IN PSA DEMONSTRATED THAT ADILUMUMAB REDUCED CAROTID INTIMAL THICKNESS BUT DID NOT CORRELATE WITH LIPID PROFILES

RESULTS: CFR (CORONARY FLOW RESERVE) INCREASED FROM 2.2 TO 3.02 AFTER THERAPY AND CORRELATED HS CRP AND TNF REDUCTION BUT NOT PASI

PSO/PSA AND EF

Study
Brezinski et al performed a systemic review that investigated EF dysfunction in PSO/PSA.

Objective
Effect of TNF inhibitors on EF in PSO/PSA

Results
- 2/3 studies demonstrated that TNF alpha inhibitors improved EF

- 2261 patients (20 studies) demonstrated:
  - Increased arterial thickness
  - Impaired endothelial vasodilatation
  - Increased carotid intima-media thickness
  - Decreased aortic elasticity
REDEFINING DIABETES

Classical Definition

A group of metabolic dzs characterized by hyperglycemia resulting from defects in insulin secretion, action or both.

Alternative Definition

**TYPE 1 DIABETES** - IMMUNE DESTRUCTION OF INSULIN PRODUCING CELLS

**TYPE 2 DIABETES** - IMMUNE SYSTEM IMPAIRING EFFECTOR CELL RESPONSE TO INSULIN.

Kaelmanda et al., the role of TNF alpha in mice with type 1&2 DM; Plos one 7(5) @33254,doi:10.1371/journal.ponc.0033254
DIABETES CARE,26:3160-67,2003
Winer et al., 2009 demonstrated that when DIO mice, which were B cell deficient, were subjected to a high cal/fat diets, did not develop insulin resistance. It was only when the mice were injected with B cells or Ig from obese insulin resistant mice, that they developed manifestations of Diabetes.

Winer studied 32 overweight people with aged matched cohort and demonstrated those with Insulin Resistance had pathogenic Antibodies.

He then went back to his preclinical mice study: He txd the mice with mouse equivalent of anti CD20. The CD20 attacked the mature B cells only.

After 1 cycle, the mice had a reduction in insulin resistance with near normal metabolism of glucose.

Winer et al., B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG Abs: Nature Medicine, published online: April 17, 2011.
Winer et al., B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG Abs; Nature Medicine, published online: April 17, 2011.

FURTHER SUPPORT

- antiCD3 Abs, IL2 Ig, mutant IL15 Ig, and rapamycin in and alpha 1 Antitrypsin
- Permanently restored euglycemia to NOD mice
- Reversed gene dysregulation in peripheral lymph nodes and stabilize c-peptide and reduce HbA1C
- PDE4 inhibitors elevate GLP-1 which lowers serum glucose as well
  NOD mice = non-obese diabetic (model for type 1 DM)
TNF GENE

Kievet, et al.,
**TNF ALPHA AS THERAPEUTIC TARGET IN DIABETES**

- **New onset T1D/T2D mice:**
  Control/short course anti TNF

- **Untreated group**
  remained hyperglycemic despite daily insulin therapy and majority died within 7 weeks of onset of T1D

- **Anti TNF Group**
  achieved euglycemia in 22/24 subjects with no deaths.

- **Anti TNF Alpha**
  has also been shown to ablate a T cell rich islet cell invasion of B cells on biopsy.

- **And in fact...**
  in 1, 35 pt study-- pts txd with TNF alpha inhibitors There was clear improvement in glycemic control.

- **Txd Group**
  decrease of FPG by 2.74mmol/L vs .02 mmol/L in control group

PSO/PSA AND DM2  Odds Ratio FROM 4 POOLED STUDIES

PSO AND DM = 1.76

PSA AND DM = 2.18

SEVERE PSO AND DM = 2.10

THE COMBINATION OF DM AND PSO LED TO MORE MICROVASCULAR COMPLICATIONS THAN DIABETES ALONE.

SO WHAT ELSE?

One Study found that:

- DM undiagnosed in 19% of PSO pts
- HTN undiagnosed in 22% of PSO pts
- Hypercholesterolemia undiagnosed in 30% of PSO pts
- 60% failed to achieve treatment targets for the CV risk factors
- PCPs –only 43% screened for HTN, 11%-dyslipidemia, 27%-DM and 30% for obesity

CV Inflammation Reduction Trial
- 7000 pts w/o inflammatory disease - TX was placebo or MTX 15-20mg/week –3-5 yrs.
- Results= no change in IL1b, IL6,hs CRP or CV events

Canakinumab Anti-Inflammatory Thrombosis Outcomes study
- 10,061 pts with previous MI and elevated CRP (>2 mg/L)
- Canakinumab 150mg/ 3 mos vs placebo-48 mos
- Initial results demonstrate a marked reductions in CV events as well as hsCRP in the active arm –despite elevated lipids
QUESTIONS

1. DO YOU BELIEVE THAT TREATMENT OF PSO WILL HAVE IMPACT ON COMORBIDITIES OF DM, HTN, SLEEP, DEPRESSION, CV DZ??

2. DO YOU BELIEVE THAT THE COROLLARY IS TRUE?

3. IF SO, HOW CAN WE IMPROVE OUR PATIENT’S OUTCOME??
Thank you