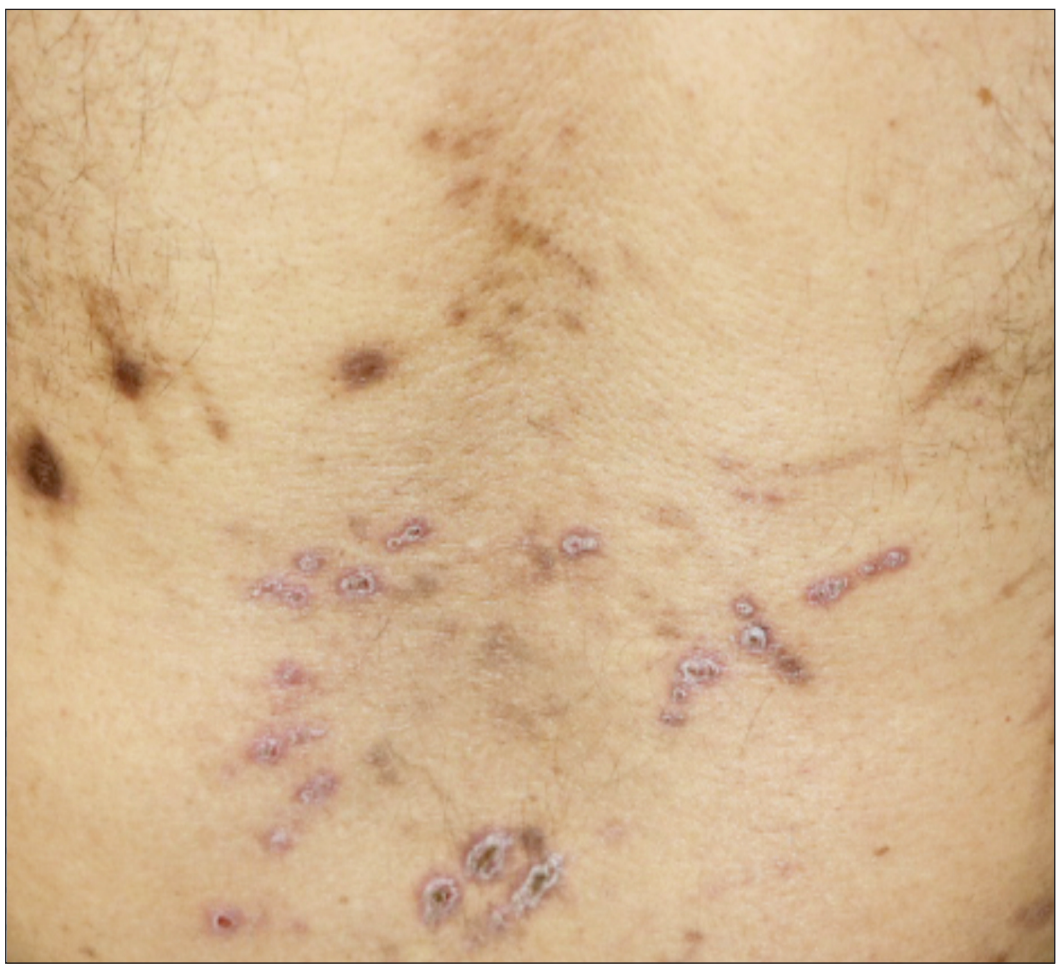
INDIAN ASSOCIATION OF DERMATOLOGISTS VENEREOLOGISTS & LEPROLOGISTS
IADVL
1973

IADVL

ISSUE 1

A Publication from IADVL Academy Special Interest Group (SIG) Pruritus



Contents

EDITORIAL

Dr.Asit Mittal

Dr.Brig Rajesh Verma

Chronic Pruritus is a debilitating symptom associated with number of dermatological, systemic, neural and psychological diseases. In recent years advances in molecular research, genetically modified models, and translation human studies have led to a better understanding of pathogenesis and treatment of chronic pruritus. It ishowever difficult to keep pace with the exponential scientific information that is emerging. Looking at the importance of this field in both clinical and academic dermatology, it is indeed very heartening thatIADVL and its Academy has recognised the importance of this very important but less discussedtopic, andgave it's go ahead for starting a special interest group(SIG) on Pruritus. The aim of this group is to disseminate current scientific knowledge in this field to the IADVL members through various means as well to stimulate basic and clinical research on Pruritus particularly in the Indian context. This News letter is an attempt in this direction. This issue contains current literature relevant to an average clinician, a guest piece on “chronic Prurigo” by Dr Sonia Stander and Dr Manuel Parera (University of Munster, Germany) two of the very well-known researchers in the field of itch and an illustrative case of neuropathic pruritus. We aim to bring out more such news letters in future on periodic basis. We hope that this small attempt on part of SIG Pruritus proves to be extremely informative to our readers and will go a long way in enhancing our understanding about various aspects of chronic pruritus

GUEST COLUMN

Chronic prurigo: a disease in its own right

Manuel P. Pereira, Sonja Ständer

Department of Dermatology and Center for Chronic Pruritus,
University Hospital Münster, Germany

Chronic pruritus, i.e. pruritus occurring for 6 weeks or longer, and a prolonged scratching behavior may lead to the emergence of hyperkeratotic pruriginous lesions. These lesions can vary substantially in their appearance, ranging from small papules to nodules, plaques or linear lesions. Chronic prurigo was recently suggested as an umbrella term embracing the vast array of clinical manifestations of this highly burdensome condition.

Of importance for the understanding of chronic prurigo, is the concept that this condition is a distinct disease and not a mere reaction pattern to scratching. Clinical and pathophysiological arguments support this claim. Susceptible patients with chronic pruritus of different etiologies and a prolonged scratching behavior develop pruriginous lesions, which are similarly distributed. Additionally, pruriginous lesions do not differ according to the underlying etiology of the pruritus and thus the origin of the pruritus cannot be deduced by the clinical manifestation of the disease. Therapeutically, the treatment of the underlying cause of the pruritus is often not enough to alleviate the chronic prurigo, which requires a specific therapy. As for the pathophysiological aspects, common mechanisms were demonstrated for chronic prurigo regardless of the origin of the pruritus. Mediators such as interleukin-31, CGRP, substance P and NGF play a role in the neuroinflammatory modulation of chronic prurigo, whilemorphologically a hypertrophy of dermal nerves and a reversible rarefication of intraepidermal nerve fibers could be demonstrated for pruriginous lesions.

Considering chronic prurigo a disease in its own right is of great importance to achieve a better care. It brings more awareness of this impairing condition to researchers and clinicians and aides in the selection of suitable patients for clinical trials testing innovative drugs.

Suggested readings

[1] Pereira MP, Steinke S, Zeidler C, Forner C, Riepe C, Augustin M, et al. European academy of dermatology and venereology European prurigo project: expert consensus on the definition, classification and terminology of chronic prurigo. J Eur Acad Dermatol Venereol 2018;32; 1059-1065.

[2] Pereira MP, Zeidler C, Nau T, Bobko S, Evers AWM, Garcovich S, et al. Position Statement: Linear prurigo is a subtype of chronic prurigo. J Eur Acad Dermatol Venereol 2019;33; 263-266.

[3] Schneider G, Driesch G, Heuft G, Evers S, Luger TA, Stander S. Psychosomatic cofactors and psychiatric comorbidity in patients with chronic itch. Clin Exp Dermatol 2006;31; 762-767.

[4] Sonkoly E, Muller A, Lauerma AI, Pivarcsi A, Soto H, Kemeny L, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol 2006;117; 411-417.

[5] Liang Y, Jacobi HH, Reimert CM, Haak-Frendscho M, Marcusson JA, Johansson O. CGRP-immunoreactive nerves in prurigo nodularis--an exploration of neurogenic inflammation. J Cutan Pathol 2000;27; 359-366.

[6] Haas S, Capellino S, Phan NQ, Bohm M, Luger TA, Straub RH, et al. Low density of sympathetic nerve fibers relative to substance P-positive nerve fibers in lesional skin of chronic pruritus and prurigo nodularis. J Dermatol Sci 2010;58; 193-197.

[7] Johansson O, Liang Y, Emtestam L. Increased nerve growth factor- and tyrosine kinase A-like immunoreactivities in prurigo nodularis skin -- an exploration of the cause of neurohyperplasia. Arch Dermatol Res 2002;293; 614-619.

[8] Schuhknecht B, Marziniak M, Wissel A, Phan NQ, Pappai D, Dangelmaier J, et al. Reduced intraepidermal nerve fibre density in lesional and nonlesional prurigo nodularis skin as a potential sign of subclinical cutaneous neuropathy. Br J Dermatol 2011;165; 85-91.

[9] Bobko S, Zeidler C, Osada N, Riepe C, Pfleiderer B, Pogatzki-Zahn E, et al. Intraepidermal Nerve Fibre Density is Decreased in Lesional and Inter-lesional Prurigo Nodularis and Reconstitutes on Healing of Lesions. Acta Derm Venereol 2016;96; 404-406.

CURRENT LITERATURE – PRURITUS AND PRURIGO


Dr. Kapil Vyas


Dr.Asit Mittal

In recent years there have been major advances in our understanding of chronic Pruritus. Number of scientific articles published on this subject in journals related to Dermatology and medicine has grown significantly. This compilation is an attempt to assimilate this vast information in a more systematic manner. For a simplified reading we have segregated the chosen articles into sub heads such as those dealing with epidemiology aspect, investigative aspect, therapeutic developments, and few related to measurement of Pruritus. The reader will thus find it easier to pick article of his /her interest.

Clinical Dermatology – Therapy

1. N Engl J Med , JAN,2020; 382;3. doi: 10.1056/NEJMe1916598

Difelikefalin for the Treatment of Uremic Pruritus

David J.R. Steele, M.B., B.Ch.
Editorial

Background :
Management of uremic pruritus is challenging. The use of specific mu opioid receptor antagonists and kappa opioid receptors agonists to treat severe uremic pruritus has been reported as effective and forms the rationale for the current trial of the drug difelikefalin, an kappa opioid receptors agonist .

Observation :
This editorial presents brief summary of a phase 3 trial of the drug difelikefalin in management of uremic pruritus in patients undergoing dialysis, (fishbane et al.).
As reported by Fishbane and colleagues, the use of difelikefalin in a population of patients undergoing in-center hemodialysis over a 12-week treatment period resulted in a significant abatement in pruritus symptoms, with a decrease of at least 3 points in the score on the 24-hour Worst Itching Intensity Numerical Rating Scale (a standard assessment scale used by the investigators to quantitate pruritus; scores range from 0 to 10, with higher scores indicating greater itch intensity), as well as a significant improvement in pruritus-related quality of life. The findings are compelling, although diarrhea, dizziness, and vomiting were frequent side effects. The risk of drug dependence was addressed, which is important because difelikefalin is an opioid peptide analogue.

Conclusion :
Although presently not approved by FDA , Phase 3 trial for difelikefalin is encouraging in management of uremic pruritus.

2. N engl j med February 2020; 382;8. doi : 10.1056/NEJMe1916733

Breaking the Itch–Scratch Cycle in Prurigo Nodularis
Shawn G. Kwatra
Editorial

Background :
Prurigo nodularis is chronic relapsing dermatoses with intense itching impairing the patient's quality of life.It has been associated with multiple comorbidities as atopy ,diabetes and renal diseases. Pathomechanism is complex and no treatment is considered gold standard.Several clinical trials are on way in hope of efficacious therapy

Observation: Stander et al. report the results of a phase 2 trial of subcutaneous injection of nemolizumab, a humanized interleukin-31 receptor A monoclonal antibody, in adult patients with prurigo nodularis and severe pruritus. The investigators chose the primary outcome to be the percentage reduction in peak pruritus severity from baseline to week 4. In the active-treatment group, there was a 53% reduction of itch in 4 weeks after a single injection of nemolizumab, as compared with a 20% reduction in the placebo group, a significant difference. Nemolizumab appeared to work rapidly, with a 25% reduction in itch by the end of the first week. Additional outcomes favoring the drug over placebo were the reduction in number of nodules, more healed lesions, and better sleep and quality of life.

Conclusion :
The results of this trial provide hope for prurigo patients with intractable itch.

3. J Am Acad Dermatol 2019 May ;80:1395-402. doi :10.1016/j.jaad.2019.01.052.

Serlopitant reduced pruritus in patients with prurigo nodularis in a phase 2, randomized, placebo-controlled trial

Sonja Stander,,Paul Kwon, Joe Hirman, Andrew J. Perlman, Elke Weisshaar, Martin Metz, ,and Thomas A. Luger

Background:
Anecdotal evidence suggests that neurokinin 1 receptor antagonism reduces pruritus
intensity in chronic pruritic conditions such as prurigo nodularis (PN).

Objective: This study assessed safety and efficacy of the neurokinin 1 receptor antagonist serlopitant for treatment of pruritus in PN.

Methods: In this randomized, double-blind, placebo-controlled study, 128 patients with chronic,
treatment-refractory PN for more than 6 weeks received serlopitant, 5 mg, or placebo orally once daily for 8 weeks. The primary end point was change in average itch visual analog scale score at weeks 4 and 8.

Results: Average itch visual analog scale scores significantly improved with serlopitant versus with placebo at weeks 4 and 8: the least squares mean difference (serlopitant minus placebo) was _1.0 at week 4 (P = .02) and _1.7 at week 8 (P\.001). The least squares mean difference between serlopitant and placebo reached statistical significance at week 2 (_0.9 [P = .011]). The most frequently reported treatment emergent adverse events in the serlopitant group were nasopharyngitis, diarrhea, and fatigue.

Limitations: The 8-week duration may be insufficient to assess clinically relevant resolution of PN lesions.

Conclusions: Serlopitant reduced pruritus in patients with treatment-refractory PN and was well tolerated.

4. Acta Derm Venereol. 2018 Jan 12;98:26-31. doi: 10.2340/00015555-2780.

Role of Substance P and Its Receptor Neurokinin 1 in Chronic Prurigo: A Randomized, Proof-of-Concept, Controlled Trial with Topical Aprepitant.

Ohanyan T , Schoepke N, Eirefelt S, Hoey G, Koopmann W, Hawro T, Maurer M, Metz M.

Background

Substance P (SP) and its receptor neurokinin 1 (NK1R) are thought to be involved in the pathogenesis of chronic prurigo.

Objective

Assessement of SP serum levels, cutaneous NK1R expression, and the effects of topical aprepitant , an NK1R antagonist, in patients with chronic prurigo.

Methods

This was a randomized, placebo-controlled, split-sided, double blind trial,A group of 46 individuals, consisting of 26 CPG patients and 20 healthy individuals, was assessed for serum levels of SP using enzyme-linked immunoassay (ELISA) . Nineteen patients with CPG were assessed for cutaneous NK1R expression with the help of immunohistochemistry of cutaneous biopsies. The primary objective was to demonstrate the efficacy of topical 1% aprepitant gel applied twice daily on pruritus in patients with CPG, compared with placebo vehicle after 28 days of treatment.outcome parameters used were Patient Global Assessment(PGA) and Visual Analogue Scale (VAS)

Results

SP and NK1R were increased, compared with controls, in the serum and in lesional vs. non-lesional skin of the patients, respectively. Aprepitant, reduced the intensity of pruritus as assessed by visual analogue scale by > 50% from baseline to day 28 (–35.2), but so did placebo vehicle (–38.1, $p = 0.76$). Overall clinical scores improved significantly by day 28 in both treatment groups, with no significant difference between the 2 groups ($p = 0.32$).

Conclusion

Findings imply that both SP and NK1R are involved in the pathogenesis of chronic prurigo. Parallel group designed trials are needed to assess the efficacy of topical aprepitant treatment in this condition.

5. J Eur Acad Dermatol Venereol. 2018 Mar;32:437-440. doi: 10.1111/jdv.14646.

Treatment of prurigo with methotrexate: a multicentre retrospective study of 39 cases.

Klejtman T, Beylot-Barry M, Joly P, Richard MA, Debarbieux S, Misery L, Wolkenstein P, Chosidow O, Ingen-Housz-Oro S.

Background:

Prurigo is a common primary pruritic condition. Treatment is challenging. Methotrexate (MTX) is effective for the treatment of pruriginous dermatoses, but its use in prurigo has been little studied.

Objectives:

To investigate the efficacy and safety of MTX in the treatment of difficult-to-treat prurigo.

Methods:

Patients from six university dermatology departments treated with MTX between 2006 and 2016 for difficult-to-treat prurigo (i.e. with failure to conventional therapies) were included in this retrospective multicentre study. Patients with other pruritic dermatoses were excluded. Clinical efficacy was recorded after 3, 6 and 12 months of treatment: (i) subjective efficacy, that is, evaluation of the pruritus by the patient and (ii) objective efficacy, that is, assessment of cutaneous lesions by the physician: complete or almost complete remission (CR) (healing of lesions), partial remission (PR) (incomplete improvement of lesions) or failure (no improvement or worsening). The overall response rate (ORR) included CR and PR.

Results:

Thirty-nine patients with previous failure of topical steroids, H1-antihistamine drugs or phototherapy were included. The median weekly dose of MTX was 15 mg (range 5-25 mg). The median follow-up was 16 months (2-108). The mean time between onset of MTX and objective efficacy was 2.4 ± 1.2 months and the mean duration of response was 19 ± 15 months. The ORR was 91% at 3 months [n = 36, CI 95% (81.2-100.8%), CR 44%], 94% at 6 months [n = 32, CI 95% (85.7-102.2%), CR 56%] and 89% at 12 months [n = 28, CI 95% (77.4-100.6%), CR 57%]. Seven patients stopped MTX because of failure, and five because of the discovery of hepatocarcinoma (n = 1), elevated transaminases (n = 1), infectious pneumonitis (n = 1) or gastrointestinal symptoms (n = 2).

Conclusion:

Methotrexate is a therapeutic option in difficult-to-treat prurigo.

6. J Am Acad Dermatol. 2018 Jun;78:1209-1211. doi: 10.1016/j.jaad.2018.02.024.

Rapid improvement of prurigo nodularis with cyclosporine treatment.

Wiznia LE, Callahan SW, Cohen DE, Orlow SJ

Background

Prurigo nodularis (PN) is a chronic skin condition characterized by pruritic nodules, representing the end-stage cutaneous changes of scratching secondary to itch. PN is often refractory to topical corticosteroids and calcineurin inhibitors, and many patients require systemic treatment.

Objectives

To observe effect of cyclosporine in prurigo nodularis

Method

A retrospective chart review was performed for patients with a diagnosis of PN or lichen simplex seen at the academic medical center based practices of 2 attending physicians (Drs Orlow and
Cohen) from 2005-2015. Patients treated with cyclosporine were included, and charts were reviewed to exclude those without clear diagnoses or treated with other therapies. Data regarding patient age, length of and dosing of cyclosporine treatment, side effects attributed to cyclosporine, whether or not remission was achieved, and time to remission were collected. In all, 76 patient charts were reviewed; 8 patients qualified for inclusion, 5 of which were female.

In 1995, Berth-Jones et al observed that PN might respond to cyclosporine, which was also observed in another study. Treatment with cyclosporine has been associated with adverse events, including creatinine elevation, hypertension, gastric upset, muscle pains, angioedema, gingival hyperplasia, and neuropathy. Siepmann et al published a report on a series of 14 patients treated with cyclosporine showing a significant response in 13 patients, 7 of whom experienced the aforementioned side effects.

Results

The average age was 57 years. With the pediatric patient excluded, the average age of included adults was 64 years.The average dose of cyclosporine was 3.1 mg/kg, and the average time until improvement was ;3 weeks. Patients reported fewer new lesions, decreased pruritus, and resolution of existing lesions. Four patients had complications attributed to cyclosporine, which included migraines, nausea, hypertension, dizziness, blurry vision, keratoacanthoma, hypercholesterolemia, and folliculitis. None had an elevation in creatinine. Six patients achieved remission, 1 was lost to follow-up, and the final patient reported significant improvement but not remission. No patients reported recurrence upon treatment discontinuation..

Conclusion

Retrospective chart review illustrates the rapid improvement cyclosporine can afford patients with PN.

7. N Engl J Med. 2017 Mar 2;376(9):826-835. doi: 10.1056/NEJMoa1606490.

Anti-Interleukin-31 Receptor A Antibody for Atopic Dermatitis.

Ruzicka T, Hanifin JM, Furue M, Pulka G, Mlynarczyk I, Wollenberg A, Galus R, Etoh T, Mihara R, Yoshida H, Stewart J, Kabashima K; XCIMA Study Group.

Background:

Interleukin-31 may play a role in the pathobiologic mechanism of atopic dermatitis and pruritus.

Objective

Assessment of the efficacy and safety of nemolizumab , a humanized antibody against interleukin-31 receptor A, in the treatment of atopic dermatitis.

Methods:

In this phase 2, randomized, double-blind, placebo-controlled, 12-week trial, adults with moderate-to-severe atopic dermatitis that was inadequately controlled by topical treatments received subcutaneous nemolizumab (at a dose of 0.1 mg, 0.5 mg, or 2.0 mg per kilogram of body weight) or placebo every 4 weeks or an exploratory dose of 2.0 mg of nemolizumab per kilogram every 8 weeks. The primary end point was the percentage improvement from baseline in the score on the pruritus visual-analogue scale (on which a negative change indicates improvement) at week 12. Secondary end points included changes in the score on the Eczema Area and Severity Index (EASI, on which a negative change indicates improvement), and body-surface area of atopic dermatitis.

Results:

Of 264 patients who underwent randomization, 216 (82%) completed the study. At week 12, among the patients who received nemolizumab every 4 weeks, changes on the pruritus visual-analogue scale were -43.7% in the 0.1-mg group, -59.8% in the 0.5-mg group, and -63.1% in the 2.0-mg group, versus -20.9% in the placebo group ($P<0.01$ for all comparisons). Changes on the EASI were -23.0%, -42.3%, and -40.9%, respectively, in the nemolizumab groups, versus -26.6% in the placebo group. Respective changes in body-surface area affected by atopic dermatitis were -7.5%, -20.0%, and -19.4% with nemolizumab, versus -15.7% with placebo. Among the patients receiving nemolizumab every 4 weeks, treatment discontinuations occurred in 9 of 53 patients (17%) in the 0.1-mg group, in 9 of 54 (17%) in the 0.5-mg group, and in 7 of 52 (13%) in the 2.0-mg group, versus in 9 of 53 (17%) in the placebo group.

Conclusions:

In this phase 2 trial, nemolizumab at all monthly doses significantly improved pruritus in patients with moderate-to-

severe atopic dermatitis, which showed the efficacy of targeting interleukin-31 receptor A. The limited size and length of the trial preclude conclusions regarding adverse events.

8. Ann Dermatol. 2016 Apr;28:159-63. doi: 10.5021/ad.2016.28.2.159.

Clinical Efficacy and Safety of Naltrexone Combination Therapy in Older Patients with Severe Pruritus.

Lee J, Shin JU, Noh S, Park CO, Lee KH.

Background:

Severe pruritus is a challenging condition, and it is more difficult to deal with in older patients due to their limitations in taking oral medication because of underlying diseases, possible interaction with concurrent medications, and poor general condition.

Objective:

To evaluated the efficacy and safety of naltrexone , an opioid antagonist, in elderly patients with severe pruritus that was not easily controlled with conventional antipruritics.

Methods:

Eighteen patients were enrolled, with a mean age of 73 years. They additionally received 50 mg of naltrexone per day for an average of 2 months.

Results:

Using the visual analogue scale, 13 (72.2%) of 18 patients showed a "much improved" condition, reporting more than a 50% decrease in pruritus intensity. Sixteen (88.9%) showed symptomatic improvement, and only 2 (11.1%) had persistent pruritus. Five patients reported side effects including insomnia, fatigue, constipation, and anorexia. However, reactions were either limited to the first 2 weeks or well managed.

Conclusion:

Naltrexone could be an effective and safe alternative treatment option to control severe pruritus in older patients.

9. J Am Acad Dermatol. 2016 Feb;74:363-9. doi: 10.1016/j.jaad.2015.09.039.

Thalidomide for the treatment of chronic refractory pruritus.

Sharma D, Kwatra SG.

Background

For pruritus with an inflammatory or autoimmune origin, therapies such as topical corticosteroids and antihistamines and additional systemic therapies are often ineffective. Thalidomide, an immunomodulator and neuromodulator, may be a useful alternative treatment.

Methods

Over the course of April to July 2015, we conducted a literature search on the National Library of Medicine, Ovid MEDLINE, and OLDMEDLINE databases for word combinations of ''thalidomide'' coupled with ''pruritus,'' ''itch,'' ''antipruritic,'' and ''urticaria.'' All of the results were recursively checked for relevance and suitability. No manufacturers or authors mentioned in these reports were contacted.

Results

Search yielded a total of 208 reports (with redundancy) from 1965 to 2014 containing the aforementioned key words. Ultimately, 33 clinical articles were included as they focused on chronic refractory pruritus. Case reports and studies concerning thalidomide analogs were excluded. In these studies, the pharmacology of thalidomide, neuronal

mechanism, and clinical antipruritic potency were often discussed. the response to thalidomide was reviewed in more than 280 patients with refractory pruritus, most often because of prurigo nodularis. Most experienced considerable relief.Peripheral neuropathy was the most common adverse event, but was frequently reversible. Thalidomide can be considered as an option for patients with treatmen t resistant pruritus

Conclusion

Considerable relief of chronic pruritus has been demonstrated with thalidomide in case reports, case series, and controlled trials.

10. J Am Acad Dermatol 2016;75:619-25. doi.:10.1016/j.jaad.2016.02.1237

Gabapentin and pregabalin for the treatment of chronic pruritus

Kazuki M. Matsuda, Divya Sharma, Ariel R. Schonfeld, Shawn G. Kwatra

Background :

Chronic pruritus is a distressing symptom that is often refractory to treatment. Patients frequently fail topical therapies and oral over-the-counter antihistamines, prompting the clinician to consider alternative therapies such as neuroactive agents. Herein, the use of gabapentin and pregabalin, 2 medications well known for treating neuropathic pain and epilepsy that are occasionally used for relieving chronic pruritus is explored. The findings from original sources published to date to evaluate the use of gabapentin and pregabalin as antipruritic agents are explored. They are found to be promising alternative treatments for the relief of several forms of chronic pruritus, particularly uremic pruritus and neuropathic or neurogenic itch, in patients who fail conservative therapies.

Methods:

We searched the PubMed database, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews for English language articles using the key words ''gabapentin,'' pregabalin,'' ''pruritus,'' and ''itch.'' Only primary sources published before October 2015 were included in the study. We have focused only on chronic itch, so we excluded studies concerning acute pruritus. One article was not included, because it was unable to be accessed. Here we define randomized controlled trials (RCTs) as randomized, placebo-controlled, and double-blinded studies, and define open-label trials (OLTs) as all other prospective experimental studies. The level of evidence and the strength of recommendation were determined using Strength of Recommendation Taxonomy system.

Results :

We identified 22 studies that used gabapentin, 12 studies that used pregabalin, and 3 studies that used both gabapentin and pregabalin. Different studies (RCT ,OLT & Retrospective Cohort studies) prove gabapentin to be effective in chronic pruritus of several causes viz. neuropathic , uremic, cholestatic cytokine related and idiopathic pruritus. Similar study designs also prove the efficacy of pregabalin in pruritus of different origin (aquagenic , uremic , drug related, traumatic and idiopathic).

Conclusion :

Gabapentinoids are efficacious and safe drugs in chronic pruritus of several etiology.

11. Dermatol Ther. 2014 May-Jun;27(3):135-9. doi: 10.1111/dth.12094.

Combination therapy of fexofenadine and montelukast is effective in prurigo nodularis and pemphigoid nodularis.

Shintani T, Ohata C, Koga H, Ohyama B, Hamada T, Nakama T, Furumura M, Tsuruta D, Ishii N, Hashimoto T.

Objective

Evaluation of the efficacy of combination therapy of second-generation antihistamine antagonist, fexofenadine hydrochloride, and leukotriene receptor inhibitor, montelukast sodium, for the treatment of prurigo nodularis or pemphigoid nodularis patients, in whom conventional therapy was ineffective.

Methods

15 patients received 10 mg montelukast once a day and 240 mg fexofenadine twice a day for 4 weeks in addition to other medications they had been taking. We assessed the manifestations of the lesions and itching intensity before and after the therapy, and we evaluated each patient as (i) markedly improved, (ii) improved, (iii) slightly improved, (iv) no change, (v) worse.

Results

Two patients (13.3%) were evaluated as markedly improved, and the lesions of one patient completely disappeared. Three patients (20.0%) were evaluated as improved, and six patients (40.0%) as slightly improved. Thus, 11 of 15 cases (73.3%) improved by combination therapy of fexofenadine and montelukast, in which nine cases (75.0%) of prurigo nodularis and two cases (66.7%) of pemphigoid nodularis were involved. No patients revealed any side effects.

Conclusion

This study revealed that combination therapy of fexofenadine and montelukast was effective for some patients with conventional therapy-resistant prurigo nodularis and pemphigoid nodularis.

12. Indian J Dermastol. 2013 Sep;58:355-9. doi: 10.4103/0019-5154.117300.

Oral ketotifen and topical antibiotic therapy in the management of pruritus in prurigo nodularis: a randomized, controlled, single-blind, parallel study.

Sharma AD.

Objective :

To evaluate the role of oral ketotifen and topical antibiotic therapy in the management of pruritus in prurigo nodularis (PN) patients.

Methods:

Twenty-seven patients with PN and a history of atopy with raised IgE were included in this study in a dermatology clinic. All patients had positive growth of Staphylococcus aureus on the lesional skin swab. All patients received topical halobetasol and oral hydroxyzine for 4 weeks. In addition, all patients in the study group received oral ketotifen and topical antibiotic therapy for 4 weeks. Randomization was performed by using a table of random numbers, and the participants were randomly allocated to one of the two groups in the study. The study was a single-blind study, and the blinding was done by the investigator.

Results:

Of the 14 patients in the study group, 9 had complete relief from pruritus by the end of first week, which was maintained till the end of 4 weeks. In the control group, mild to moderate reduction in the intensity of pruritus in the PN lesions of all patients were noted by the end of the first week. No further improvement in the level of pruritus was noted in the participants during the trial period. The treatment was well tolerated by the patients, and the adverse reactions of drugs were minimal in both groups.

Conclusions:

This study showed that oral ketotifen and topical antibiotic therapy can be helpful in the management of pruritus in PN patients.

13. J Clin Pharm Ther. 2013 Feb;38:16-8. doi: 10.1111/jcpt.12005.

Treatment of prurigo nodularis with pregabalin.

Mazza M, Guerriero G, Marano G, Janiri L, Bria P, Mazza S.

Background

Prurigo nodularis (PN) is a chronic skin condition that is difficult to treat. Pregabalin is one of the possible treatments for PN but its safety and efficacy are not well defined.

Objective

We aimed to assess the efficacy of pregabalin in patients with PN.

Methods:

Thirty patients (10 men, 20 women; mean age 51.6 ± 9.39 years) were treated with pregabalin (75 mg/day) for 3 months. Efficacy was classified as (i) successful (disappearance of the pruritus and reduction of nodules); (ii) slight improvement/reduction of the nodules, that is, number and/or flattening, no disappearance of itching; or (iii) unsuccessful.

Results:

Twenty-three patients (76%) responded successfully after 3 months of treatment. There was a statistically significant difference between visual analogue scale scores before and after 1 month treatment period (8·15 ± 2·04 and 1·5 ± 1·12, respectively; $P < 0·0001$). Pregabalin was generally well tolerated with only six (20%) patients reporting side effects. No patient showed any renal insufficiency.

CONCLUSION:

Study shows pregabalin was effective for the treatment of PN.

CLINICAL DERMATOLOGY –EPIDEMIOLOGICAL STUDIES OF PRURITUS

14. Journal of Investigative Dermatology (2020) 140, 568e573; doi:10.1016/j.jid.2019.05.034

Itch and Mental Health in Dermatological Patients across Europe: A Cross-Sectional Study in 13 Countries

Florence J. Dalgard, Ake Svensson, Jon Anders Halvorsen, Uwe Gieler, Christina Schut, Lucia Tomas-Aragones et al

Background :
Itch is a highly prevalent and multidimensional symptom.chronic itch negatively impact the mental health and overall quality of life

Objective :
Analysis of the association between itch and mental health in dermatological patients.

Methods :
This multicenter study is observational and cross-sectional and was conducted in dermatological clinics across 13 European countries. A total of 3,530 patients and 1,094 healthy controls were included. Patients were examined clinically. Outcome measures were itch (presence, chronicity, and intensity), the Hospital Anxiety and Depression Scale, EQ-5D visual analogue scale, sociodemographics, suicidal ideation, and stress (negative life events and economic difficulties). Ethical approval was obtained.

Results:
Study revealed significant association between the presence of itch in patients and clinical depression (odds ratio, 1.53; 95% confidence interval, 1.15e2.02), suicidal ideation (odds ratio, 1.27; 95% confidence interval, 1.01e1.60), and economic difficulties (odds ratio, 1.24; 95% confidence interval, 1.10e1.50). The mean score of reported generic health status assessed by the EQ-5D visual analogue scale was 65.9 (standard deviation = 20.1) in patients with itch, compared with 74.7 (standard deviation = 18.0) in patients without itch (P < 0.001) and 74.9 (standard deviation ¼ 15.7) in controls with itch compared with 82.9 (standard deviation =15.6)
in controls without itch (P < 0.001).

Conclusion:
Itch contributes substantially to the psychological disease burden in dermatological patients, and the management of patients should include access to multidisciplinary care.

15. J Am Acad Dermatol. 2020 Jan;82 :34-36. doi: 10.1016/j.jaad.2019.09.007.

Analysis of real-world treatment patterns in patients with prurigo nodularis.

Huang AH, Canner JK, Kang S, Kwatra SG.

Background :
Management of prurigo remains challenging.Till now, no therapies have been approved or standardized guidelines has been formulated for the treatment of PN.There is a need to understand real-world treatment practices for these patients.

Objective :
Describing treatment patterns in patients with PN using claims data from a large ambulatory cohort in the United States.

Methods :
Longitudinal records (October 2015 through December 2016) from the IBM MarketScan Commercial Claims and Encounters Database (IBM Watson Health; IBM, Armonk, NY) were analyzed. Adults (86,855) aged 18 to 64 years with at least 2 medical claims for PN (7095): were compared to those without PN age- and sex-matched control individuals (16,595), patients with atopic dermatitis (AD) (23,882) , and patients with psoriasis (38,283) . Treatments of interest based on literature and clinical experience were identified by using the National Drug Codes (Red Book) and Current Procedures Terminology codes.

Results :
The most commonly prescribed therapies for patients with PN included corticosteroids: intralesional (36.4%), topical (26.1%), and systemic (19.0%). Among neuropsychiatric medications prescribed to patients with PN, gabapentin (6.5%) was used most frequently. Patients with PN were less likely to receive topical or systemic steroids and calcineurin inhibitors or phototherapy but more likely to receive intralesional steroid injections compared with patients with AD or psoriasis .Nonsteroidal, skin-directed therapies were rarely explored in patients with PN. Phototherapy is an option with efficacy demonstrated to be superior to that of clobetasol that may be underused in PN compared with other inflammatory skin.

Conclusion:
Real time treatment practices are useful in revealing practice gaps in prurigo treatment and may aid in developing better therapeutic guidelines in near future.

16. J Am Acad Dermatol 2019 April ;80:931-7. doi : 10.1016/j.jaad.2018.08.044.

Association between itch and cancer in 16,925 patients with pruritus: Experience at a tertiary care center

Valerie A. Larson, Olive Tang, BS, Sonja Stander, Sewon Kang, Shawn G. Kwatra, MD

Background:
Pruritus has been associated with cancer. However, limited data are available on the types of underlying malignancies associated with pruritus.

Objective:
To characterize the association between pruritus and different cancer types, as well as variations by racial group.

Methods:
Cross-sectional study of patients ≥18 years of age seen at the Johns Hopkins Health System during 2013-2017. Patients with pruritus were compared with patients without pruritus. Analyses were stratified by race.

Results:
Patients with pruritus were more likely to have concomitant malignancy than those without pruritus (odds ratio 5.76, 95% confidence interval 5.53-6.00). Most strongly associated were cancers of the liver, gallbladder and biliary tract, hematopoietic system, and skin. Compared with white patients, black patients more frequently had soft tissue, dermatologic, and hematologic malignancies and less frequently had liver, respiratory, gastrointestinal, and gynecologic malignancies.

Limitations:
The cross-sectional design precludes analysis of the temporal association between pruritus and malignancy. The study is limited to a single tertiary care center.

Conclusion:
Pruritus is most strongly associated with cancers of the liver, skin, and hematopoietic system. Black patients with pruritus have a higher likelihood of skin, soft tissue, and hematologic malignancies than white patients, while whites have higher likelihoods of liver, respiratory, gastrointestinal, and gynecologic malignancies.

17. J Am Acad Dermatol. 2014 Apr;70(4):651-658. doi: 10.1016/j.jaad.2013.11.045.

Five-year malignancy incidence in patients with chronic pruritus: a population-based cohort study aimed at limiting unnecessary screening practices.

Fett N, Haynes K, Propert KJ, Margolis DJ.

Background:

The incidence of malignancy in patients with chronic pruritus and nondiseased skin is unknown.

Objective:

We sought to assess the hazard ratio (HR) of incident overall malignancy and incident malignancy by subtype in patients with chronic pruritus during the 5 years after diagnosis.

Methods:

A population-based cohort study was performed in the Health Improvement Network. In all, 8744 patients with chronic pruritus were matched with 31,580 patients without chronic pruritus based on sex, age, and practice. Primary outcomes were HR of incident malignancy and HR of malignancy subtypes.

Results:

The fully adjusted HR for incident malignancy in patients with chronic pruritus was 1.14 (95% confidence interval 0.98-1.33). The fully adjusted HR for incident hematologic malignancy and incident bile duct malignancy in patients with chronic pruritus was 2.02 (95% confidence interval 1.48-2.75) and 3.73 (95% confidence interval 1.55-8.97), respectively. The incidence of hematologic malignancy and cholangiocarcinoma in patients with chronic pruritus was 0.0016 and 0.0003 per person-year, respectively.

Limitations:

Potential for misclassification and detection biases is a limitation.

Conclusions:

Chronic pruritus without concomitant skin changes is a risk factor for having undiagnosed hematologic and bile duct malignancies, but not other malignancies. The overall incidence of these malignancies in patients with chronic pruritus is very low.

CLINICAL DERMATOLOGY -REVIEW ARTICLES

18. J Am Acad Dermatol 2020;82:1205-12. doi : 10.1016/j.jaad.2020.01.036

Cannabinoids for the treatment of chronic pruritus: A review

Christina Avila, Susan Massick, Benjamin H. Kaffenberger, Shawn G. Kwatra,
Mark Bechtel

Background :
The endocannabinoid system plays an important role in skin homeostasis in addition to broader effects on neurogenic responses such as pruritus and nociception, inflammation, and immune reactions. Clinical studies have shown the efficacy of cannabinoids in pruritus of several dermatologic and systemic diseases.

Review:
Cannabinoids represent a broad class of endogenous and exogenous arachidonic acid-derivative compounds with activity at the cannabinoid receptors, CB1 and CB2 and the transient receptor potential (TRP) ion channels. It has

been shown to modulate the endogenous endocannabinoid system (ECS) and have shown promising antipruritic effects due to a combination of effects on neuronal activation, transmission along the afferent pathway, and local modulation of keratinocyte and mast cells. Increased activity of cannabinoid at both CB1 and CB2 have been shown to alleviate pruritus.Cannabinoids disrupt neurogenic inflammation through TRPV1 antagonism or stabilization of the ion channel. CB1 and CB2 receptor are widely expressed in peripheral immune cells, and their activation decreases inflammation, in experimental models of dermatitis.Clinical trials of cannabinoids for pruritic diseases has proved their efficacy in pruriceptive itch, such as dermatitis, neurogenic itch in metabolic derangements, and chronic intractable itch in prurigo. Topical treatments of PEA and adelmidrol (a PEA analog) significantly reduced inflammation and pruritus in a large observational study and in a small open-label study after patients with atopic dermatitis applied the cannabinoid-containing cream for 4 weeks. Topical application of a derma-membrane system based lotion combined with anandamide and PEA for 3 weeks decreased pruritus in patients on hemodialysis, and by the end of the study, itch was completely eliminated in nearly one-half of the patients. Dronabinol, a synthetic THC, was incidentally reported to provide short-term relief in 3 patients with intractable pruritus secondary to chronic liver disease. Owing to the studies that show that the antipruritic effect of cannabinoid agonists is partly due to cannabinoid receptors in the central nervous system, systemic cannabinoids may be optimal for severe itch whereas topicals would only address peripheral mechanisms. Studies with smoked/aerosolised marijuana products has been shown effective for management of neuropathic pain, which suggests it has promise for treating pruritus but at the compromise of systemic adverse effects. cannabinoid-containing topical are of particular interest in skin disease because of the high safety profile and direct, local application to involved areas, To date, systemic effects have not been reported after topical application of cannabinoids, and furthermore, many of the antipruritic effects of cannabinoids were shown using non-THC cannabinoids (CBD, PEA), eliminating the concern for undesired psychoactive effects.

Conclusion : Given the complexity of the ECS and the heterogeneity of cannabinoid structure and function, cannabinoids may have different effects depending on the origin of the pruritus, and future research will hopefully provide more mechanistic precision. Interpretation of clinical studies, however, is limited by the lack of double-blinded controlled clinical trials and by the variation in cannabinoid products, delivery methods, and formulations. Despite the limited number of published studies, trials done at present have shown consistent improvement in pruritus in the setting of multiple diseases.

19. J Am Acad Dermatol 2019 March ;80:756-64. doi : 10.1016/j.jaad.2018.09.020.

A systematic review of evidence-based treatments for prurigo nodularis

Azam A. Qureshi ,Laura E. Abate, Gil Yosipovitch, Adam J. Friedman,

Background

Prurigo nodularis is a chronic dermatologic condition involving the development of multiple cutaneous nodules in the setting of intractable pruritus. Given emerging treatment options for this difficult-to-treat condition, a current review of therapeutics is needed.

Objective

Review of evidence-based treatments for prurigo nodularis

Method

A systematic review was performed for clinical studies investigating prurigo nodularis treatment published from 1990 to present including ≥5 subjects. A total of 35 articles were assigned a level of evidence according to the Oxford Center for Evidence-based Medicine.

Results
All 5 studies investigating topical agents, including corticosteroids, calcineurin inhibitors, calcipotriol, and capsaicin, conveyed some beneficial effect with level of evidence 2b or higher. Six of 8 reports investigating photo- and photochemotherapy achieved levels of evidence 2b or greater and showed good partial response rates. Thalidomide was studied by 6 reports providing evidence of good symptom response, only 2 of which were rated level 2b or greater. Cyclosporine and methotrexate have demonstrated benefit in 4 combined studies, albeit with level 4 evidence. Pregabalin, amitriptyline, paroxetine, fluvoxamine, and neurokinin-1 receptor antagonists have demonstrated promising evidence in 5 level 2b studies.

Conclusion
Higher-powered studies and additional randomized controlled trials are needed for the evaluation of safe and efficacious systemic treatment options for prurigo nodularis.

20. J Eur Acad DermatolVenereol 2018 july;32:1059-65.doi:10.1111/jdv.14570

European academy of dermatology and venereologyEuropean prurigo project: expert consensus on the definition, classification and terminology of chronic prurigo

Pereira MP, Steinke S, Zeidler C, Forner C, Riepe C, Augustin M, Bobko S, Dalgard F, Elberling J, Garcovich S, Gieler U, Gonçalo M, Halvorsen JA, Leslie TA, Metz M, Reich A, Şavk E, Schneider G, Serra-Baldrich E, Ständer HF, Streit M, Wallengren J, Weller K, Wollenberg A, Bruland P, Soto-Rey I, Storck M, Dugas M, Weisshaar E, Szepietowski JC, Legat FJ, Ständer S; EADV Task Force Pruritus group members.

Background
The term prurigo has been used for many decades in dermatology without clear definition, and currently used terminology of prurigo is inconsistent and confusing. Especially, itch-related prurigo remains unexplored regarding the epidemiology, clinical profile, natural course, underlying causes, available treatments and economic burden, although burdensome and difficult to treat.

Objective
To address these issues, the multicentre European Prurigo Project (EPP) was designed to increase knowledge on chronic prurigo (CPG). In the first step, European experts of the EADV Task Force Pruritus (TFP) aimed to achieve a consensus on the definition, classification and terminology of CPG. Additionally, procedures of the cross-sectional EPP were discussed and agreed upon.

Methods
Discussions and surveys between members of the TFP served as basis for a consensus conference. Using the Delphi method, consensus was defined as an agreement ≥75% among the present members.

Results
Twenty-four members of the TFP participated in the consensus conference. Experts consented that CPG should be used as an umbrella term for the range of clinical manifestations (e.g. papular, nodular, plaque or umbilicated types). CPG is considered a distinct disease defined by the presence of chronic pruritus for ≥6 weeks, history and/or signs of repeated scratching and multiple localized/generalized pruriginous skin lesions (whitish or pink papules, nodules and/or plaques). CPG occurs due to a neuronal sensitization to itch and the development of an itch-scratch cycle.

Conclusion

This new definition and terminology of CPG should be implemented in dermatology to harmonize communication in the clinical routine, clinical trials and scientific literature. Acute/subacute forms of prurigo are separated entities,which need to be differentiated from CPG and will be discussed in a next step. In the near future, the crosssectional EPP will provide relevant clinical data on various aspects of CPG leading to new directions in the scientific investigation of CGP.

EXPERIMENTAL STUDIES-PRURITUS

21. Journal of Investigative Dermatology (2020) 140, 203e211; doi:10.1016/j.jid.2019.05.029

Peripheral Sensitization and Loss of Descending Inhibition Is a Hallmark of Chronic Pruritus

Esther M. Pogatzki-Zahn, Manuel P. Pereira, Alexander Cremer, Claudia Zeidler, Tim Dreyer, Claudia Riepe, Carola Wempe, Tobias Lotts, Daniel Segelcke, Matthias Ringkamp, Andreas E. Kremer, Konstantin Agelopoulos and Sonja Stander

Background :

Neurophysiological mechanisms leading to chronicity of pruritus are not yet fully understood and it is not known whether these mechanisms diverge between different underlying diseases of chronic pruritus (CP).

Objectives :

To detect pathophysiological mechanisms of peripheral sensitization and central inhibition involved in the development and maintenance of CP, and whether these mechanisms diverge between CP of different origins.

Methods :

A total of 120 patients with CP of inflammatory origin (atopic dermatitis), neuropathic origin (brachioradial pruritus), and chronic prurigo of nodular type, the latter as a model for chronic scratching, as well as 40 matched healthy controls participated in this study. In this study we used a comprehensive set of neurophysiological and morphologic investigations, both in patients with CP and healthy matched controls, to determine the impact of different peripheral pruritus pathways, as well as the involvement of endogenous inhibition by condition pain modulation (CPM) for various entities of CP.

Results :

Stimulation with cowhage induced a more intensive itch sensation compared with stimulation with other substances in all patient groups but not in healthy controls, arguing for sensitization of cutaneous mechanoand heat-sensitive C-fibers in CP. All patient groups showed a decreased intraepidermal nerve fiber density compared with controls. A decreased condition pain modulation effect was observed in all patient groups compared with controls, suggesting a reduced descending inhibitory system in CP.

Conclusion :

CP of different etiologies showed a mixed peripheral and central pattern of neuronal alterations, which might contribute to the chronicity of pruritus with no differences between pruritus entities.

22. Journal of Investigative Dermatology (2019) 139, 2245e2248; doi:10.1016/j.jid.2019.04.007

Where Is Itch Represented in the Brain, and How Does it Differ from Pain? An Activation Likelihood Estimation Meta-Analysis of Experimentally-Induced Itch

Carl A. Roberts, Timo Giesbrecht , Andrej Stancak, Nicholas Fallon, Anna Thomas and Tim C. Kirkham

Background :
Itch and pain sensations exhibit a substantial anatomical overlap with common peripheral transmission and recruited brain regions. recent functional magnetic resonance imaging (fMRI) studies have observed activations in the pain-processing network during cowhage- or histamine induced itch. the differences in brain processing of these two types of sensation have yet to be satisfactorily determined.

Method :
Conducting activation likelihood estimation (ALE) meta-analysis of experimentally induced itch from the published fMRI literature and generation of a comparison ALE map of experimental pain (using the previously reported coordinates of Tanasescu et al., 2016), to conduct meta-analytic conjunction/ contrast analyses between the two sensations.
Analyses were performed using Brainmap GingerALE, version 2.3.6 (Research Imaging Institute, San Antonio, TX).We adhered to the ALE method devised by Eickhoff et al. (2009, 2012), with the correction devised by Turkeltaub et al. (2012). The P-values in our analyses were generated by 10,000 permutations. We used a cluster-level family-wise error correction at $P < 0.05$ to correct for multiple comparisons, following an initial cluster forming threshold of uncorrected $P < 0.001$

Result :
ALE meta-analysis included all studies reporting whole brain fMRI analysis of experimentally induced itch (histamine, cowhage, or electrical stimulation). Data were pooled from a total of 11 experiments (from10 papers,with a total of 117 participants and 313 reported foci).Significant clusters were observed in the thalamus, left frontal operculum cortex/insular cortex, and right frontal operculum cortex/ insular cortex. There was a high degree of overlap in brain activation for itch and pain in the conjunction analysis. conjunction analysis showed substantial overlap between itch and pain in the thalamus, insula and frontal operculum. However, areas of the left and right thalamus showed significant differences in convergence between itch and pain, supporting the proposals that variation in itch and pain perception can found in subregions of the thalamus.

Conclusion :
Thalamus and the affective areas of the anterior insula/ frontal operculum are consistently activated across fMRI studies that induce itch experimentally.

Comment : Once considered submodality of pain, pruritus has been experimentally proven as a distinct somatosensory modality with significant overlap with pain in terms of neuroanatomy

23. Journal of Investigative Dermatology (2019) 139, 971-973; doi:10.1016/j.jid.2018.09.032

Non-Histaminergic Itch Mediators Elevated in the Skin of a Porcine Model of Scabies and of Human Scabies Patients

Kristen M. Sanders, Leigh A. Nattkemper , Jordan D. Rosen , Hjalte H. Andersen , Jeremy Hsiang , Paolo Romanelli , Charlotte Bernigaud , Jacques Guillot , Olivier Chosidow , Gil Yosipovitch

Background :
Scabies itch is intense and worsens at night. Though, histamine was considered as important mediator , scabetic itch was found refractory to antihistamine treatment. The molecular mechanisms of scabies itch are still unknown.

Objectives :
To investigate the potential mechanisms of scabies itch.

Methods :
Samples were collected from scabies-infested and healthy control skin of pigs and humans. Three female Sus scrofa domesticus "large white" pigs were used for the experiment. Biopsies were taken from areas of lesional, mite-infested skin and non-lesional mite-free skin along the back and neck. Human samples included de-identified skin biopsies from 6 scabies patients and 4 healthy control volunteers Biopsies were taken from the abdomen. For scabies patients, diagnosis was confirmed by visualization of mites via microscopy of lesional skin adjacent to the tissue used for this study. Using immunohistochemistry, we quantification of the itch mediators TRPV1, TRPA1, PAR-2, tryptase, and histamine in both pig and human samples were done . quantification of b-tubulin were done in order to identify changes in ENFD (epidermal nerve fibre density).

Results :
In the porcine model , epidermal expression of TRPV1, TRPA1, and PAR-2 was increased in tissue infested with scabies (P = 0.031, P < 0.0001, and P = 0.002, respectively). The number of tryptase þ cells near the dermal- epidermal junction was increased in porcine tissue infested with scabies (P =0.021). The number of histamine cells did not differ between scabies-infested and control skin (P = 0.73). ENFD did not differ between scabies and control tissue (P =0.059). In human samples, epidermal expression of TRPV1, TRPA1, and PAR-2 was elevated in scabies infested tissue compared to healthy control (P = 0.002, P = 0.027, and P = 0.010, respectively). Furthermore, the number of tryptase cells near the dermal-epidermal junction was increased in human tissue infested with scabies (P = 0.043). However, the number of histamine þcells near the dermaleepidermal junction was decreased in scabies-infested tissue (P ¼=0.003). ENFD was elevated in human skin infested with scabies (P = 0.037).

Conclusion:
There is significant elevations of nonhistaminergic itch mediators in the skin of a pig model experimentally infested with scabies and of human scabies patients.

Comment : Predominant involvement of non histaminergic mediators in scabetic pruritus recommend against the widespread use of antihistamines in scabies.

24. Journal of Investigative Dermatology (2019) ; doi:10.1016/j.jid.2019.06.130

Elevated Blood Cadmium and Lead Levels in Chronic Pruritic Dermatoses

Sagar P. Patel, Raveena Khanna, Micah Belzberg, Sewon Kang ,Shawn G. Kwatra

Background :
Skin pollutants including heavy metals can impair cutaneous barrier function, activate inflammatory pathways, induce oxidative stress, and influence the immune response .These changes in turn may give rise to chronic pruritic dermatoses.

Objectives :
Investigation of the association between chronic pruritic skin eruptions and blood levels of cadmium, lead, and mercury.

Methods :
We first conducted a literature review using EMBASE, PubMed, and MEDLINE, with the following keywords: heavy

metals, cadmium, lead, skin, rash, pruritus, and itch. We also conducted a cross-sectional analysis of the data from the National Health and Nutrition Examination Survey study, which was collected by the National Center for Health Statistics from 2005 to 2006 and approved by its institutional review board. Presence of chronic pruritic dermatoses was assessed by participants answering affirmatively to having "an itchy rash which was coming and going for at least 6 months" This cohort was compared both to participants reporting asthma, and a healthy control group without asthma or pruritic dermatoses. Blood samples were taken and stored as per required protocol Heavy metal measurements in blood were made with a Perkin Elmer (model SIMAA 6000) simultaneous multielement atomic absorption spectrometer and inductively coupled plasma-mass spectrometer.

Results :

Our literature review yielded 1,221 articles after removing duplicates. Although increased blood heavy metal levels were not found to be associated with eczema, increased exposure to lead (P = 0.008), copper (P=0.04), and zinc (P =0.01) was associated with more severe eczema. Tannery workers with increased serum chromium (P < 0.05) were found to have increased cutaneous complaints of rough skin, itch, and rash (P < 0.001. study investigating arsenic found that increased exposure was associated with more severe hyperkeratotic skin lesions and pruritus (P < 0.05). In our National Health and Nutrition Examination Survey analysis, there were 10,348 survey respondents. We excluded 1,941 participants lacking laboratory data and 260 participants with incomplete questionnaires. Of the 8,147 eligible subjects with complete data, 473 (5.8%) reported chronic pruritic dermatoses. Mean blood cadmium levels were 18.4% (P = 0.0039) higher in pruritic dermatoses compared with healthy controls, and 8.3% (P =0.26) higher than asthma patients. Mean blood lead levels in pruritic dermatoses were 9.9% (P = 0.0366) higher than healthy controls, and 28.2% (P < 0.0001) higher than asthma patients. Mean blood mercury levels in pruritic dermatoses were 11.2% (P = 0.1023) and 20.5% (P = 0.0270) higher than healthy controls and asthma patients, respectively. Multiple logistic regression, adjusted for age, sex, race, education, asthma, and smoking status, showed an association between pruritic dermatoses and increased blood cadmium levels (odds ratio =1.23; 95% confidence interval =1.02-1.48). A separate multiple logistic regression using the same variables also identified an association with increased blood lead levels (odds ratio =1.07; 95% confidence interval = 1.01-1.13). An association with mercury levels was not observed (odds ratio =1.03; 95% confidence interval = 0.97-1.09;

Conclusion :

Physicians should consider screening patients presenting with chronic pruritic dermatoses of uncertain etiology for pollution exposure given the association of elevated lead and cadmium levels in these patients.

25. Journal of Investigative Dermatology (2018) 138, 1843-1850; doi:10.1016/j.jid.2018.02.019

Persistent Extracellular Signal-Regulated Kinase Activation by the Histamine H4 Receptor in Spinal Neurons Underlies Chronic Itch

Kun Huang, Dan-Dan Hu, Dong Bai, Ze-Yang Wu, Yi-Yang Chen, Yi-Jun Zhang, Xin Lv, Qing-Xiu Wang and Ling Zhang

Background :

Transient extracellular signal-regulated kinase (ERK) activation in the spinal cord triggers histamine-induced acute itch. However, whether persistent ERK activation plays an important role in chronic itch development remains unclear.

Objective :

This study investigated the role of spinal ERK activation in chronic itch.

Result :
The results showed that repetitive DNFB (2,4-dinitrofluorobenzene) painting on the nape of mice evoked not only initial scratching but also sustained, spontaneous scratching. In addition, DNFB induced itching rather than nociception, as demonstrated using a cheek model. Furthermore, ERK was persistently activated in the spinal cord of DNFB-treated mice, and the intrathecal inhibition of phosphorylation of ERK suppressed both spontaneous itching and ERK activation.
ERK activation was observed in neurons but not in glia cells during chronic itch development. Finally, DNFB induced spontaneous itching behavior and ERK activation were largely inhibited by the histamine H4 receptor antagonist JNJ7777120 but not by the H1 receptor antagonist chlorpheniramine.

Conclusion :
Our results indicate that persistent ERK activation via the histamine H4 receptor in spinal neurons underlies DNFB-induced chronic itch.

26. Journal of Investigative Dermatology (2018) 138, 1311-1317; doi:10.1016/j.jid.2017.12.029

The Genetics of Chronic Itch: Gene Expression in the Skin of Patients with Atopic Dermatitis and Psoriasis with Severe Itch

Leigh A. Nattkemper, Hong Liang Tey, Rodrigo Valdes-Rodriguez, Helen Lee,
Nicholas K. Mollanazar, Christian Albornoz, Kristen M. Sanders , Gil Yosipovitch

Objective :
Identifying itch-related mediators and receptors that are differentially expressed in pruritic skin,

Methods :
RNA sequencing was used to analyze the complete transcriptome in skin from paired itchy, lesional and nonitchy, nonlesional skin biopsies from 25 patients with atopic dermatitis and 25 patients with psoriasis and site-matched biopsies from 30 healthy controls. This analysis identified 18,000 differentially expressed genes common between itchy atopic and psoriatic skin compared with healthy skin.

Observations :

Almost 2,000 genes were differentially expressed between itchy and nonitchy skin in atopic and psoriatic subjects. Overexpression of several genes, such as phospholipase A2 IVD, substance P, voltage-gated sodium channel 1.7, and transient receptor potential (TRP) vanilloid 1, in itchy skin was positively correlated with itch intensity ratings in both atopic dermatitis and psoriasis. Cytokines such as IL-17A, IL-23A, and IL-31 had elevated gene transcript levels in both itchy atopic and psoriatic skin. However, expression of genes for TRP vanilloid 2, TRP ankyrin 1, protease-activated receptor 2, protease-activated receptor 4, and IL-10 was found to be increased only in pruritic atopic skin, whereas expression of genes for TRP melastatin 8, TRP vanilloid 3, phospholipase C, and IL-36a/g was elevated only in pruritic psoriatic skin.

Conclusion :
This “itchscriptome” analysis will lead to an increased understanding of the molecular mechanisms of chronic pruritus and provide targets for itch treatment irrespective of disease state.

27. J Am Acad Dermatol January 2020 Volume 82, Issue 1, Pages 80–86 doi.:10.1016/j.jaad.2019.06.043

Validity and Reliability of Itch Assessment Scales for Chronic Pruritus in Adults:A Prospective Multicenter Study

Yong Hyun Jang , Seok Min Kim, Dong Hyuk Eun, , Kyung Duck Park, Gyeong-Hun Park, Byung-Soo Kim et al .

Background:
Several tools can provide a reliable and accurate evaluation of pruritus, including the visual analogue scale (VAS), numeric rating scale (NRS), verbal rating scale (VRS), and multidimensional questionnaires such as the itch severity scale (ISS). However, no single method is considered a gold standard.

Objective:
We evaluated the validity and reliability of VAS, NRS, VRS, and ISS and their correlation with a pruritus-specific quality of life instrument, ItchyQoL.

Methods: A total of 419 patients with chronic pruritus (215 men and 204 women, mean age of 46.58 years) recorded their pruritus intensity on VAS, NRS, VRS, and ISS. Retest reliability was analyzed in a second assessment (3 hours after the initial assessment). All participants answered ItchyQoL.

Results: A strong correlation between VAS, NRS, and VRS was found. ISS showed a low intercorrelation validity with these tools. However, ISS was more strongly correlated with ItchyQoL. The retest reliability scores were similar for VAS, NRS, and VRS but lower than that obtained for ISS.

Limitations: Limitations include patient heterogeneity and recall bias.

Conclusion: The assessment of pruritus is challenging because of the subjective symptoms and the multifactorial nature. Therefore, more studies are needed to determine the best strategy to assess itch intensity.

Comment : Despite the development of various Validated and Reliable scientific tool for assessment of pruritus , this area of science is still in its infancy.

28. Journal of Investigative Dermatology (2019) 139, 264-269; doi:10.1016/j.jid.2018.12.004

Research Techniques Made Simple:Itch Measurement in Clinical Trials

Stephen Erickson and Brian S. Kim

Abstract :
Chronic itch is a highly prevalent and debilitating symptom. Dramatic advances in the treatment of chronic itch, or itch lasting longer than 6 weeks, have increased the need for itch evaluation in the clinical research setting.Itch can be evaluated via subjective patient reported assessment of itch intensity (e.g., numerical rating scale, visual analogue scale) or by objective measurement of scratching activity and scratching-induced skin changes (e.g.,actigraphy, physician assessment). The unidimensional itch intensity scales (e.g., NRS, VRS, and VAS) provide simple, reliable, and valid measures of itch intensity that have successfully been used in large-scale clinical trials but as Itch is a complex, multifactorial entity with profound effects on quality of life, multidimensional assessments of patient wellbeing (e.g., ItchyQoL) provide valuable information. Current limitations of subjective measures of itch include the need for optimization and further delineation of a clinically meaningful level of improvement. Objective measurement of itch is promising but currently requires cautious interpretation. New apps and tools may greatly improve compliance and provide more objective measurements of itch in the future.

29. Journal of Investigative Dermatology (2018) 138, 1062e1068; doi:10.1016/j.jid.2017.11.028

Validation of Scratching Severity as an Objective Assessment for Itch

Jeremy Udkoff1 and Jonathan I. Silverberg

Background :
There are currently no simple, standardized, objective assessments of itch for clinical trials and practice.

Objective:
To validate and test the severity of scratching as an objective measure of itch (4-point ordinal scale ranging from 0 [not present] to 3 [very prominent] based on the observation of scratching lesions).

Methods :
This was a prospective outpatient study using questionnaires and evaluations by a dermatologist in adults with atopic dermatitis (n = 261). We enrolled subjects between January 2014 and January 2017 with different stages of disease activity and disease severities ranging from clear to severe. We re-evaluated patients at each consecutive visit, and they were allowed to complete any number of the possible symptom instruments.[NRS,VRS,5-D itch scale, DLQI etc]. Kendall tau-B rank correlation coefficients were determined for severity of scratching with NRS-itch in the past 24 hours and 3 days, 5-D itch scale, NRS-pain in the past 7 days, NRS-sleep in the past 3 days, DLQI, mean ItchyQoL, POEM, VRS-itch in the past 2 weeks, and patient-reported global AD severity. Responsiveness and change over time were tested using Spearman rho correlation coefficient for directionality of each symptom severity scale based on visit number.
The nonparametric Wilcoxon rank-sum or Mann-Whitney U tests were used to compare continuous values of NRS-itch in the past 24 hours and 3 days; 5-D itch scale, NRS-pain in the past 7 days; NRS-sleep in the past 3 days; DLQI, mean ItchyQoL, and POEM across different levels of scratching severity. Fisher exact test was used to compare the ordinal variables VRS-itch in the past 2 weeks and patient-reported global AD severity with scratching severity.
Outliers were detected using Tukey's method , and sensitivity analyses were performed that excluded outliers. Post hoc correction for multiple dependent tests were performed by minimizing the false discovery rate with the approach of Benjamini and Hochberg (1995) and corrected P-values are presented. Two-sided corrected P values less than 0.05 were considered statistically significant.

Observation:
Severity of scratching best correlated with patient-reported global atopic dermatitis severity (Kendall ϯ = 0.336, P < 0.0001), numeric rating scale of itch in the past 24 hours (ϯ = 0.266, P = 0.0010) and 3 days (ϯ =0.296, P < 0.0001). Severity of scratching showed responsiveness over time. Patients experiencing improvement of scratching severity of 1 point or greater had significantly lower itch based on numeric rating scale in the past 3 days (Wilcoxon rank sum test, P = 0.0175), 5-D itch scale (P =0.0146), and Patient-Oriented Eczema Measure scores (P =0.0146). There was a significant decrease in scratching severity for patients experiencing itch improvement of 4 points or greater in the past 3 days on the numeric rating scale (Fisher exact test, P = 0.0026), Patient-Oriented Eczema Measure (P < 0.0001), and Dermatology Life Quality Index (P =0.0285). Severity of scratching may be a useful endpoint in clinical trials and practice across the gamut of pruritic disorders. Future studies are needed to validate severity of scratching in other pruritic disease.

Conclusion :
Severity of scratching may be a useful endpoint in clinical trials and practice across the gamut of pruritic disorders. Future studies are needed to validate severity of scratching in other pruritic disease.

AN ILLUSTRATIVE CASE OF PRURITUS

Dr. Prabhakar Sangoli

Dr. Asit Mittal

Neuropathic itch as a sole manifestation of carpal tunnel syndrome

A 62 yrs old female presented to a dermatology clinic with complaints of itching over both palms for a period of 2 months.The symptoms were more severe on right palm . Itching was mixed in character with accompanied elements of burning and tingling sensations.Itching was present throughout the day with worsening at night and was disturbing her sleep. Patient had a history of diabetes mellitus and hypertension for last 20 yrs ,for which she had been on multiple medications including Glimepride, metformin ,Rosuvastatin , Olmesartan , hydrochlorthiazide and Teneligliptin (recently introduced). Her Diabetes was under reasonable control. Her kidney and liver functions were normal. Palmer itch was treated with oral antihistamines (both sedative and non sedative), topical steroids and withdrawal of suspected drugs like teneligliptins and glimepride, without any improvement. A consultation was sought from a neurologist who thought of a diagnosis of Carpel tunnel syndrome but was uncomfortable with severe itch as the only manifestation of Carpel Tunnel Syndrome. He also advised Nerve Conduction studies of median and ulnar nerves which was refused by patient. She was then given a trial of gabapentin in a dose of 300mg twice daily but the drug was withdrawn with almost no response after 2 weeks. She was then advised to wear a wrist splint for a period of 2 weeks [Figure 1]. Within 48 hours patient reported marked improvement in her itching after wearing wrist splint and this was the only intervention which actually provided her with any relief. The case was diagnosed as neuropathic itch due to carpal tunnel syndrome and further evaluated with magnetic resonance imaging of wrist and to rule out secondary causes of carpal tunnel syndrome .

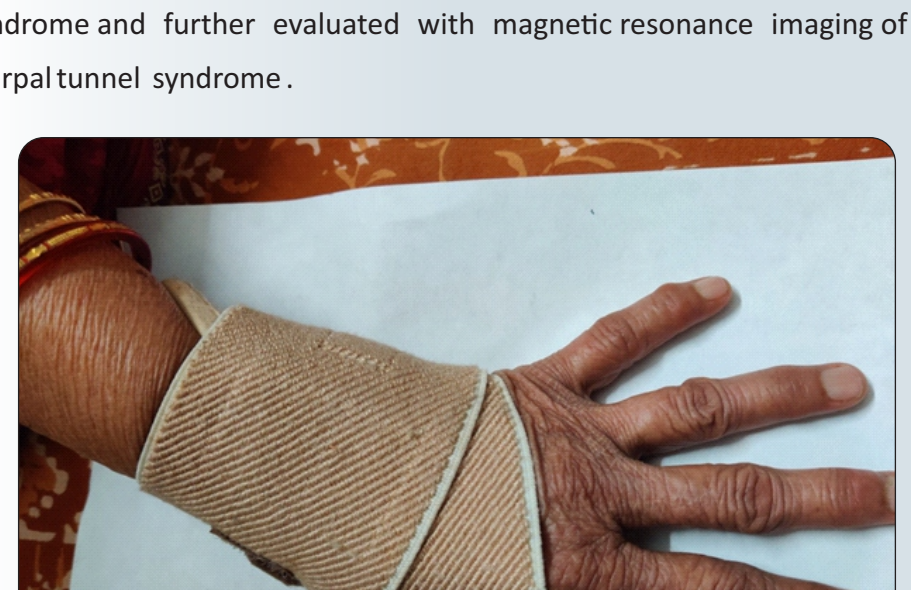


Figure 1. Wrist splint worn by patient for relieving neuropathic itch due to carpal tunnel syndrome.

Carpal tunnel syndrome is one of the nerve entrapment syndrome, that usually presents with pain , paraesthesis and local dysautonomia. It is very unusual for it to present predominantly with itch.Neuropathic itch refers to any anatomical dysfunction along the itch pathway that results in a feeling to scratch. 8% to 19% patients with chronic itch have underlying Neuropathic cause . A distinctive characteristic of neuropathic itch is the coexistence of other sensory symptoms as burning, tingling, stinging and heat and cold sensations. Disorders associated with neuropathic itch includes post herpetic neuralgia, nostalgia paraesthetica, small fiber polyneuropathies, trigeminal neuropathy, stroke and Multiple Sclerosis. This case emphasises that itch as a sole manifestation of nerve entrapment syndrome may not be rare and neuropathic cause should always be kept in mind when a clinician is confronted with localised itch of undetermined origin.

Suggested reading

1. Nabil Kanaan , R A Sawaya.Carpal tunnel syndrome: modern diagnostic and management techniques. British Journal of General Practice. 2001;51: 311-4.

2. Anne Louise Oaklander, Neuropathic Itch Semin Cutan Med Surg. 2011 Jun; 30(2): 87–92.

IADVL Office Bearers

IADVL ACADEMY - 2020

Chairperson (2020-21): Dr. Deepika Pandhi **Convener (2020-21):** Dr. Dipankar De

EX-OFFICIO MEMBERS

Dr. Kiran Godse (President)
Dr Jayadev Betkerur (President Elect)
Dr Rakhesh SV (Hon. Treasurer)
Dr Seetharam KA (Imm. Past Academy Chairperson)
Dr.Sunil Dogra (Editor, IDOJ)
Dr P. Narasimha Rao (Imm.Past President)
Dr Feroz K (Hon. Secretary General)
Dr Umashankar Nagaraju (Imm. Past Hon. Secretary General)
Dr Shashikumar BM ((Imm. Past Hon. Treasurer)
Dr.Saumya Panda (Editor, IJDVL)

MEMBERS

Dr Ananta Khurana
Dr Meghana M Phiske
Dr Rashmi Jindal
Dr G. Manmohan
Dr Nilay Kanti Das
Dr Santoshdev P. Rathod
Dr Kanthraj GR
Dr Renu George
Dr Sumit Sen
Dr Krishna Talukdar
Dr Raghunatha S
Dr Usha Khemani

IADVL

PRESIDENT
Dr. Kiran Godse

IMM. PAST PRESIDENT
Dr. P. Narasimha Rao

PRESIDENT ELECT
Dr Jayadev Betkerur

VICE PRESIDENTS
Dr. Manjunath Shenoy
Dr. Rashmikant Shah

HON GEN SECRETARY
Dr. Feroze K.

HON. TREASURER
Dr. Rakhesh SV

HON JOINT SECRETARY
Dr. Anuradha Babu
Dr. Venkatachalam K

Design & Layout by :

CBS

CBS Publishers & Distributors Pvt. Ltd.

Dedicated to Education

Branches : New Delhi · Bengaluru · Chennai · Kochi · Kolkata · Mumbai

Resident Rep. : • Bhubaneswar • Dehradun (UttaraKhand) • Giridih (Jharkhand) • Hyderabad • Nagpur • Patna • Pune • Vijayawada

www.cbspd.com