Arbeitskreis Pruritusforschung (AKP)

Protokoll der Tagung des AKP im Rahmen der Tagung der Arbeitsgemeinschaft Dermatologische Forschung (ADF)
am 18. Februar 2010, 10.00-12.45 Uhr

Tagunsort: Musik- und Kongresshalle, MuK
Willy-Brandt-Allee 10, D – 23554 Lübeck

Raum: MUK, Seminar 1-2

Programm
Vorsitz: Sonja Ständer, Thomas Mettang, Elke Weisshaar

10.00 – 10.30 Key lecture (30 min)

1. **R. Paus**: Hairy matters' in the itch circus: Lessons for pruritus research from the hair follicle

10.30 – 11.00 Uhr: Short talks I (je 10 min)

2. **C. Blome et al.:** Patients' needs in pruritus treatment
3. **K. Krause et al.:** German ItchyQoL: a novel instrument to assess pruritus-specific quality of life
4. **N.Q. Phan et al.:** Assessment of pruritus intensity: correlation between visual analogue scale (VAS), numeric rating scale (NRS) and verbal rating scale (VRS) in patients with chronic pruritus

11.30 – 12.30 Uhr: Short talks II (je 10 min)

5. **F. Pfab et al.:** Influence of acupuncture on type I hypersensitivity itch and the wheal and flare response in adults with atopic eczema – a blinded, randomized, placebo-controlled, crossover trial
6. **T. Lotts et al.:** Multidimensional Database for Pruritus Patients – statistical evaluation of clinical characteristics
7. **U. Matterne et al.:** A multidisciplinary Training Programme for Patients with Chronic Pruritus: Outline and preliminary results
8. **U. Raap et al.:** The novel T-cell cytokine IL-31 modulates the functional activity of eosinophil granulocytes in humans **- leider erkrankt-**
9. **A.E. Kremer et al.:** Autotaxin and its product, lysophosphatidic acid, are potential mediators of cholestatic pruritus

M. Schmelz, T. Mettang: Verleihung des Nachwuchs- Preises an Andreas E. Kremer
freundlicherweise gestiftet von der Firma Stiefel

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der Deutschen Dermatologischen Gesellschaft e.V. und der Arbeitsgemeinschaft Dermatologische Forschung (ADF)

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Patients' needs in pruritus treatment

C. Blome, M. Augustin, S. Ständer

Aim: To determine treatment needs in pruritus from the patients' perspective.
Methods: Important treatment goals were determined by means of (1) an open questioning of n=50 pruritus patients on their impairments and treatment goals and (2) subsequent expert discussions. The goals were implemented into the questionnaire 'Patient Benefit Index' assessing the importance the goals to the patients. N=247 patients treated at the Department of Dermatology, Münster, or participating in clinical studies in Münster filled in the questionnaire. The percentage of patients to whom the goals were at least 'somewhat' important was calculated. Importance rates were compared between age groups (median split) and gender.
Results: 27 different treatment goals were included in the Patient Benefit Index.
53.8% of the patients filling in the questionnaire were female; the average age was 56.6 years.
The most frequent goals were to be free of itching (98.0%), to find a clear diagnosis and therapy (97.2%), to have confidence in the therapy (95.5%), to be less dependent on doctor and clinic visits (83.0%), to have no fear that the disease will become worse (81.0%), and to be able to sleep better (80.2%).
The goal of being able to wear all types of clothing was more frequent in women (59.2% vs. 45.0%, p=0.028), whereas men more often aimed to be able to have more contact with other people (52.7% vs. 36.4%, p=0.011).
Patients younger than 58 years more often wanted to be able to lead a normal working life (54.5% vs. 17.4%, p<0.001) and a normal sex life (47.2% vs. 32.5%, p=0.020). To patients aged 58 years or older, it was more important to be able to have more contact with other people (51.8% vs. 36.1%, p=0.015).
Conclusion: There are various different treatment goals in patients with pruritus, some of which differ between older and younger patients and between women and men. These individual differences should be taken into account in treatment evaluation and in treatment choice in daily practice.

German ItchyQoL: a novel instrument to assess pruritus-specific quality of life

K. Krause, B. Keßler, M. Maurer, M. Metz

Pruritus is a widely spread symptom in numerous dermatologic and systemic diseases that may have an enormous impact on patients' daily life. The high individual burden of chronic pruritus along with the difficulty in objectively measuring pruritus intensity makes the assessment of quality of life (QoL) a suitable instrument to evaluate the impact of itch upon a patient and the efficacy of its therapy. To date, a QoL instrument that addresses the particular aspects most relevant for pruritus patients which can be applied in pruritus independent of the underlying cause is lacking in German-speaking countries. Recently, the first existing pruritus-specific QoL questionnaire (ItchyQoL) has been created by Desai et al. and proven to be reliable, valid and responsive. In order to develop a German version of the instrument, we translated, culturally adapted and retranslated the original instrument in cooperation with the original authors and performed pilot testing. This resulted in the creation of the first German tool for the assessment of QoL in patients suffering from pruritus. Clinical validation of the questionnaire in a large population of patients with pruritus of any aetiology is ongoing and will enable us to explore the impact of pruritus on QoL. To date, 271 pruritus patients with different underlying diagnoses (79x urticaria, 56x atopic dermatitis, 34x psoriasis, 24x prurigo nodularis, 20x kidney disease, 13x liver disease, 11x malignancies, 34x others/unknown origin) have completed the questionnaire. Preliminary data show that women are affected more often by pruritus than men (ratio 1.8:1) but there are no major differences in mean itch severity between sexes (females 5.3, males 4.8 on a visual analogue scale [VAS] ranging from 0-10) or diseases (ranging from VAS 4.8 for urticaria to VAS 6.2 for liver disease). Future use of this patient-related outcome measure will improve efficacy of treatment in pruritus patients and generate direct patient benefit.

Assessment of pruritus intensity: correlation between visual analogue scale (VAS), numeric rating scale (NRS) and verbal rating scale (VRS) in patients with chronic pruritus

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The most commonly used tool for self-report of itch intensity is the visual analogue scale (VAS). Similar measurement tools are the numeric rating scale (NRS) and verbal rating scale (VRS). We herein present data of the first study in which reliability and concurrent validity of VAS, NRS and VRS in chronic pruritus were investigated. 200 randomly selected patients of our out-patient department (88 m, 112 f, mean 62.06 years) recorded their pruritus by VAS (10 cm line), NRS (0-10) and a four-point VRS scale. 25 patients stated no itching on VAS=0 (mean point difference [MPD] to NRS 0.70), 113 patients rated itching as low on VAS (0.1-3.9, mean 1.45; MPD 0.52), 25 patients as moderate on VAS (4.0-7.9, mean 5.58; MPD -0.02) and 18 patients as severe pruritus on VAS (8.0-10, mean 8.76; MPD -0.26). Pearson's correlation coefficient for VAS with NRS was 0.939. On the VRS, 26 patients stated to have no itch ("0") which was scored on average as 0.11 (VAS) and 0.10 (NRS). 96 patients stated to have low ("1") pruritus (mean VAS/mean NRS: 1.36/1.90), 54 patients to have moderate ("2") pruritus (mean VAS/mean NRS: 4.28/4.83) and 16 patients to have severe ("3") pruritus (mean VAS/mean NRS: 8.79/8.56). 9.5% did not record their pruritus intensity by VAS, 2.5% not by NRS and 4.0% not by VRS. Spearman's correlation coefficient for VAS with VRS was 0.788 and for NRS with VRS 0.859; $p<0.01$. In sum, NRS and VAS showed a very high correlation and concurrent validity with a low point difference of mean 0.39, SD 0.96. Thus, both scales can be used in clinical trials to assess valid data of itch intensity course. The NRS is easier to understand and handle for patients; VAS needs detailed explanations. The VRS with both VAS and NRS also showed moderate to high correlation and concurrent validity; however, the discrimination of itch intensity on the VRS is not as sensitive as on VAS and NRS.

Influence of acupuncture on type I hypersensitivity itch and the wheal and flare response in adults with atopic eczema – a blinded, randomized, placebo-controlled, crossover trial

F. Pfab [1, 2], J. Huss-Marp [1, 2], A. Gatti [1, 2], J. Fuqin [1], G. Athanasiadis [1], D. Irnich [3], U. Raap [4], H. Behrendt [2], J. Ring [1], U. Darsow [1, 2]
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Background: Itch is a major symptom of allergic skin disease. Acupuncture has been shown to exhibit a significant effect on histamine-induced itch in healthy volunteers. We investigated the effect of acupuncture on type I hypersensitivity itch and skin reaction in a double-blind, randomized, placebo-controlled, crossover trial.
Methods: A skin prick-test (house dust mite or grass pollen) was applied to 30 patients with atopic eczema before (direct effect) and after (preventive effect) two experimental approaches or control observation: acupuncture at points Quchi and Xuehai (verum acupuncture (VA), dominant side), "placebo-point" acupuncture (PA, dominant side), no acupuncture (NA). Itch intensity was recorded on a visual analogue scale. After 10min, wheal and flare size and skin perfusion (via LASER-Doppler) were measured at the stimulus site and the validated Eppendorf Itch Questionnaire (EIQ) was answered.
Results: Mean itch intensity was significantly lower in VA (35.7±6.4) compared to NA (45.9±7.8) and PA (40.4±5.8) regarding the direct effect; and significantly lower in VA (34.3±7.1) and PA (37.8±5.6) compared to NA (44.6±6.2) regarding the preventive effect.

In the preventive approach mean wheal and flare size were significantly smaller in VA (0.38±0.12cm2 / 8.1±2.0cm2) compared to PA (0.54±0.13cm2 / 13.5±2.8cm2) and NA (0.73±0.28cm2 / 15.1±4.1cm2), and mean perfusion in VA (72.4±10.7) compared to NA (84.1±10.7). Mean EIQ ratings were significantly lower in VA compared to NA and PA in the treatment approach; and significantly lower in VA and PA compared to NA in the preventive approach.
Conclusions: Acupuncture at the correct points showed a significant reduction of type I hypersensitivity itch in patients with atopic eczema. With time the preventive point-specific effect diminished with regard to subjective itch sensation, whereas it increased in suppressing skin prick reactions.

Multidimensional Database for Pruritus Patients – statistical evaluation of clinical characteristics

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A descriptive, multidimensional database was programmed to survey the demographics, diseases and clinical characteristics of chronic pruritus patients. The database contains besides demographic data a large set of pruritus characteristics such as skin-condition, localisation, course and quality of pruritus. To date, the new installed database comprises 501 patients with chronic pruritus (240 m, 261 f, mean age 60.5 years). Next to itch, half of the patients describe the quality of the symptom to be mixed with burning (51.3%) or stinging (42.3%). 50.3% of the patients feel alleviation of itch by scratching, whereas itch increases through scratching in 36.3%, reflecting alloknesis, or turns into burning (22%). Nearly half the patients presented without scratch lesions (45.6%), about 19.3% showed single scratch lesions and 34.6% had multiple scratch lesions including prurigo nodularis. The itch occurs mostly at daytime (48.5%) or in the evening (44.9%), respectively nights (42.9%). Pruritus trigger factors are especially pressure (39.1%) and touch (34.9%), followed by sweating (34.1%) and emotional stimuli (32.5%). Initially the pruritus was restricted in most patients to single areas (localized pruritus; 67.7%), which switched in the course of the disease into generalized pruritus (77.2%). Pruritus occurred mainly on the trunk (64.1%), the arms (71.5%) and the legs (71.9%). The itch intensity was measured by the visual analog scale from 0 to 10. The intensity was rated rather high by the patients since the mean value was 7.1 and the worst itch intensity in average 8.8. The data evaluation allows a deeper understanding of the course and characteristics of chronic pruritus and the patients´ perception of the symptom. Most interestingly are the different pruritus quality perceptions which may point to differentiated modulation of itch sensation. Recently, mechano-sensitive nociceptors (CMH) were demonstrated to represent another pathway for the itch sensation. Cowhage activates CMH and induces itch along with a stinging quality. It may therefore be speculated that the patients of our collective reporting on stinging quality (42.3%) have an involvement of the CMH cutaneous nerve fibers in itch induction. The impairment of the symptom by mechanical stimuli such as pressure and tough as observed in up to 40% of our patients further supports this hypothesis. An in-deep analysis of pruritus causes and therapeutic responses in these patients may lead to identification and characterization of new subgroups and pruritus pathways.

A multidisciplinary Training Programme for Patients with Chronic Pruritus: Outline and preliminary results

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Chronic pruritus (> 6 weeks) is a worldwide symptom and a burden in many dermatological, systemic and psychosomatic/psychiatric diseases. Patients with chronic pruritus frequently endure a long and complicated disease course, failure of therapy and a substantial reduction in quality of life. Psychological mechanisms may be involved in eliciting and coping with chronic pruritus. Treatment of pruritus aims to be aetiological, but as a primary illness it is symptomatic. The needs of patients with chronic pruritus are diverse. Multi-disciplinary educational and psychological training programmes aim to improve patients' understanding of the disease, raise motivation to apply more adaptive self-care measures, and consequently improve quality of life.
A multidisciplinary training consisting of dermatological, health-educational and psychological modules and based on the needs of patients with chronic pruritus was developed. The programme comprises four weekly meetings lasting two hours each and has been offered to 44 individuals so far. The programme provides information about the medical fundamentals of the skin, the multi-factorial nature of pruritus, current diagnostic procedures, the epidemiology of pruritus and therapeutic avenues for the relief of pruritus. Patients also learn about and discuss more adaptive behavioural response patterns to pruritus and the interrelationship between stress and pruritus. An established relaxation technique is practised. During all modules patients are encouraged to share their experiences with other patients. All 44 patients evaluated the four session programme. Of these 17 also completed a quality of life (QoL) instrument, measures of psychological functioning and rated the pruritus severity before and after the training.
Patients rated the programme as a highly expedient means to increase their understanding of pruritus and felt empowered to better deal with the pruritus sensation in daily life. QoL measured by the ItchyQoL improved somewhat. The Hospital Anxiety and Depression Scale (HADS), used as a measure of psychological functioning, was subject to little change. The severity of pruritus as measured by the visual analogue scale appeared better after the training. Maintenance of health through educational programmes, such as the one presented here, can be considered an important complementary measure in the field of medicine and psychosomatics, which should also be applied to patients with chronic pruritus. Preliminary results suggest improvements in QoL and reported pruritus severity.

The novel T-cell cytokine IL-31 modulates the functional activity of eosinophil granulocytes in humans

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Background: The novel T-cell derived cytokine IL-31 has been described for the induction of severe pruritus and dermatitis in transgenic mice. In humans we could recently show that IL-31 levels are increased in atopic dermatitis and correlate with disease severity.
Aim: In atopic dermatitis, eosinophil granulocytes represent key target effector cells, thus we thought to investigate the functional role of IL-31 on eosinophils.
Methods: Peripheral blood eosinophils were isolated by CD16 negative selection (purity >98%). IL-31 receptor A expression was analyzed with FACS analysis and Light-Cycler PCR, Ca^{2+} mobilization was determined fluorometrically; superoxid anion release was analyzed by lucigenin-

dependent chemiluminescence; apoptosis, CD69 surface expression and CXCL8 release with FACS analysis; and STAT-3 phosphorylation with Western Blot.
Results: Highly purified peripheral blood eosinophils expressed the IL-31 receptor A. IL-31 stimulation led to a significant increase of Ca^{2+} influx, a significant release of superoxide anions and CXCL8 of eosinophils. Further, IL-31 increased the surface expression of CD69 on peripheral blood eosinophils, whereas eosinophil apoptosis was not modified. Finally, IL-31 stimulation led to a phosphorylation of the downstream signaling molecule STAT-3.
Conclusion: Together, these data give first evidence for a functional role of IL-31 on peripheral blood eosinophils, thus revealing novel implications for IL-31 action.

Autotaxin and its product, lysophosphatidic acid, are potential mediators of cholestatic pruritus

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Pruritus is a disabling symptom in patients with cholestatic liver disorders. Bile salts and opioids have, among others, been held responsible for the induction of pruritus, but a relation with itch intensity could never be established.
Purpose: We hypothesized that potential pruritogens accumulate in the circulation of cholestatic patients and activate neurons either by (in)direct stimulation. To identify potential pruritogens we screened sera of pruritic cholestatic patients for activation of different neuronal cell lines.
Methods: Cytosolic free calcium $(Ca^{++})_i$ was measured in neuronal cell lines by ratiometric fluorimetry upon exposure to diluted serum samples of patients with intrahepatic cholestasis of pregnancy (ICP; n=33), pregnant controls (PC; n=29), patients with other causes of cholestasis (mainly PBC; n=52) and healthy subjects (HC; n=202). The $(Ca^{++})_i$ inducing factor in pruritic serum was identified by analytical techniques including quantification by HPLC-MS, autotaxin activity and bile salts by enzymatic assays, and autotaxin protein by western blot. □-Opioid activity was assayed by receptor binding assay. In mice scratch activity after intradermal pruritogen injection was quantified using a magnetic device.
Results: Transients in $(Ca^{++})_i$ in human SH-SY5Y neuroblastoma cells, induced by PBC and ICP sera were higher than those of corresponding controls. On the basis of physicochemical properties, lysophosphatidic acid (LPA) could be identified as major $(Ca^{++})_i$ agonist in pruritic sera. Serum LPA concentrations were significantly increased only in those cholestatic patients that suffered from pruritus. LPA injected intradermally into mice, induced scratch responses. Serum autotaxin (ATX) is the enzyme that converts lysophosphatidylcholine into LPA. ATX was markedly and significantly increased in sera of ICP patients vs. PC ($p<0.0001$) and in sera from pruritic cholestatic patients vs. HC ($p<0.0001$). There was a highly significant correlation ($p<0.0001$, n=52) between the serum ATX activity and the intensity of pruritus, quantified by VAS. In PBC patients who underwent nasobiliary drainage both itch intensity and autotaxin activity significantly decreased during drainage and returned to increased levels when pruritus had returned. Neither total bile salt concentrations nor μ-opioid activity correlated with itch intensity. Conclusion: Our data suggest that autotaxin and its product, LPA, play a key role in cholestatic pruritus. We speculate that ATX inhibitors may be useful as antipruritic agents in treatment of cholestatic pruritus.

Ankündigung

2. Münsteraner Pruritussymposium

- 17. / 18. 09. 2010
- Freitag ab 14.00 Uhr: Neurophysiologie
- Samstag: klinische Schwerpunkte

Organisation
Prof. Dr. S. Ständer, Prof. Dr. T.A. Luger

gemeinsam mit der Ärztekammer Westfalen-Lippe

und dem Arbeitskreis Pruritusforschung (AKP)
der DDG und der ADF