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SPECIAL REPORT

Facing the Challenges of Chronic Pruritus: A Report From a Multidisciplinary Medical Itch Centre in Germany

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The complex nature and difficult-to-establish aetiology of chronic pruritus (CP) makes it challenging to provide medical care for patients with CP. This challenge can only be met with a multidisciplinary approach. The first multidisciplinary Itch Centre in Germany was established at the University of Münster in 2002 to meet the needs of this patient population. More than 2,500 outpatients and 400 inpatients are diagnosed and receive treatment each year. To ensure evidence-based medical care, an electronic system for medical documentation and patient-reported outcomes was established. Automated data transfer to a research database enables comprehensive data analysis. Our translational research has characterized peripheral and central itch mechanisms, provided novel clustering of CP patients, and identified novel target-specific therapies (e.g. neurokinin 1 receptor-antagonist). The multidisciplinary approach, combined with basic, clinical and translational research, enables comprehensive medical care of patients as well as implementation of high-quality experimental and clinical studies. ***Key words: Competence Center Chronic Pruritus; itch clinics; prurigo nodularis; brachioradial pruritus; aprepitant; nerve fibre density; substance P; neurodermatology.***

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Pruritus (also known as itch) is a frequent cutaneous symptom that is associated with a desire to scratch (1–3). Chronic pruritus (CP) is defined as the long-term presence of the symptom (i.e. duration of 6 weeks or greater) and occurs in various diseases (3–5). CP results in a reduced quality of life (QoL), with patients experiencing issues including sleep disturbance, scratch lesions accompanied by a sense of shame, emotional burden (desperation and fear), and even psychiatric disorders (e.g. depression) (6–9). Because of these conditions, patients require multi-pronged medical care, including identification and treatment of the underlying disease and adjunct therapy for sleep disturbance and psychiatric symptoms. A specialized centre addressing the specific needs of CP patients was not available until 2002 when we established the itch clinic in Germany, the first of its kind worldwide. Our interdisciplinary centre unites 6 specialties (anaesthesiology, dermatology, internal medicine, neurology, psychosomatics, and radiology). Today, we treat more than 2,500 out-patients and 400 in-patients per year. This papers reports on the structure of our centre and on major insights in pathophysiology and treatment of CP, which were made possible by running this interdisciplinary centre.

THE PROBLEM OF ITCH AND THE NEED FOR A SPECIALIZED CENTRE

CP is a high incidence and prevalence symptom of dermatologic, systemic (including drug-related pruritus), malignant, neurological and psychiatric diseases (4, 10, 11). CP induces a high burden in patients (12). In the Global Burden of Disease (GBD) Study, pruritus was categorized among the top 50 most prevalent diseases (not only skin but all diseases) worldwide and thus carries a high burden, especially among the elderly population (2). There are several implications for the medical care of these patients in view of the following facts: (*i*) no age limit for CP occurrence exists; (*ii*) CP lacks a uniform history; (*iii*) a uniform clinical phenotype is not evident; (*iv*) a uniform pattern of sensory itch characteristics does not exist; (*v*) no unique biomarkers or diagnostic procedures are available; (*vi*) diagnostics must consider several different potential underlying diseases; and (*vii*) uniform therapy does not exist.

To take care of all these issues, specialized centres that offer comprehensive diagnostics and therapy of CP are mandatory. Patients need individual age- and disease-adapted acquisition of history, diagnostics and therapy. Because it is challenging to take an individualized approach with every patient and obtain all aspects of a patient's history in an out-patient clinical setting, we developed and established several systems to aid in patient care. These systems include modular questionnaires, elec-

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tronic systems to gather physician and patient-reported data that are collected in our clinical information system (Orbis©, Agfa Healthcare), and a diagnostic algorithm based on the results of the clinical investigation.

STRUCTURE AND CLINICAL WORKFLOW OF THE ITCH CENTRE MÜNSTER

Documentation of patient history and disease course are essential to ensure constant, high-quality care. This information is also vital for further use in quality management and clinical research. Therefore, we developed a thorough and standardized documentation concept using a consensus approach (13) based on state-of-the-art medical informatics methods. The set of forms, primarily used to collect pruritus data during routine treatment, consists of the following patient-based and physician-based documents: (*i*) an initial patient itch questionnaire (Münster NeuroDerm questionnaire); (*ii*) patient questionnaires generating scores about QoL, anxiety, depression; (*iii*) medical history forms from the first and follow-up appointments. These forms collect diagnostic and therapy information, including type of pruritus, co-morbidities, medication as well as the therapeutic response; and (*iv*) a medical report summarizing the patient case to aid in communication with the referring practitioner or other specialists.

Patient-based documentation is primarily collected in electronic format using mobile devices that are proven to be user-friendly and cost-effective (14). While patients are waiting to see the doctor, their completed questionnaires are analysed to provide scores on QoL, pruritus intensity and other patient-reported outcomes (PRO) (Fig. S1[1]). This information is then automatically transferred into the electronic health record (EHR) and can be immediately accessed by the treating physician during the patient's visit. For instance, when a certain score threshold is achieved in an anxiety and depression questionnaire, a psychosomatic consultation is recommended, which is one of the services included in the interdisciplinary work of the itch centre. The initial and the follow-up medical histories are directly entered into the local EHR; the forms are structured with catalogue selections, checkboxes and dedicated text fields to facilitate the documentation process. The physician-in-chief is permitted to determine the diagnosis. This workflow ensures that the data-set is reviewed before it is automatically pseudonymized and transferred into a separate so-called x4T research database (15). Previously, we used an Excel-based pilot database that was manually filled with data (16). The current web-based patient registry includes now > 3,000 patients from our centre. These data can be exported for complex statistical analyses.

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Challenges in the diagnostic work-up of chronic pruritus patients

Once CP is established, an appropriate diagnostic work-up is performed to identify the underlying cause of pruritus. In CP patients with normal skin, systemic, neurological and psychogenic diseases, as well as drug intake, may be the underlying causes of CP. Chronic kidney and liver diseases are the most frequently observed systemic diseases in association with CP. In some patients, a neoplastic disease is the cause of CP (10, 17). Thus, a comprehensive step-by-step diagnostic procedure is implemented to detect the underlying disease (5, 18). Laboratory analyses focus on the detection of frequent metabolic diseases and include parameters for the identification of neoplastic diseases (e.g. lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), liver enzymes and renal function parameters). A full blood cell count is performed because several haematological malignancies (e.g. polycythemia vera) are frequently associated with CP. We extracted data for 3,100 patients from our database, of whom 2,083 had a complete analysable dataset. Relevant anomalies were found in the laboratory values of 75.3% ($n = 1{,}569$) of our CP patients. Furthermore, CP patients undergo imaging tests as part of the diagnostic work-up. Depending on the history and presumed diagnosis, chest X-ray and ultrasound (abdomen and lymph nodes) are standard procedures at our clinic. Other imaging modalities, such as computed tomography (CT), positron emission tomography – computed tomography (PET-CT) and magnetic resonance imaging (MRI), are used to aid in a clear diagnosis. Of 2,083 patients, 920 received radiological diagnostics. Ultrasound examination discovered malignancies in 1% and metastases from a previously diagnosed malignant disease in 0.3% of patients. Of the patients undergoing chest X-ray, malignancies were identified in 1.7% of these patients. CT was used in 74 patients, and revealed relevant pathologies in 71.6% of the patients. Among these patients, 14.9% were newly diagnosed with a malignant tumour or metastases of a previously diagnosed malignant tumour. In total, malignancy was detected in 1.3% ($n = 27$) of all 2,083 patients. Interestingly, our results are in line with a recent paper investigating the hazard ratio of malignancies in CP patients in USA (10). MRI is particularly useful for the diagnosis of neuropathic pruritus; here, it is very important to correlate the localized MRI results with the pruritic dermatomes (19–21). Brachioradial pruritus (BRP; itching sensations on the dorsolateral aspect of the forearm) is a common example of neuropathic CP related to nerve compression caused by neuroforaminal stenosis or root compressions (22–24). From August 2008 to August 2013, a total of 136 patients with CP and suspected BRP underwent MRI examination. The cervical spine MRI displayed a strong correlation between nerve compression and the pruritic dermatomes indicated by the patient (87.9% of all patients).

Psychosomatic aspects should not be neglected in the diagnostics. Using a consecutive sample of 109 dermatologic in-patients from our centre, 1–6 psychiatric/psychosomatic diagnoses could be demonstrated in > 70% of the CP patients. A predominant psychologically induced pruritus of the dissociative or somatoform disorder was diagnosed in only 5.5% of patients. In more than 60% of the patients, psychotherapeutic or psychiatric treatment was recommended. In contrast, approximately 90% of the patients reported no previous psychotherapeutic experience (9).

PATIENTS' CHARACTERISTICS AND RESULTING INFORMATION ON PREVALENCE AND UNDERLYING DISEASES

Analysis of the database data enables a deeper understanding of the characteristics of CP patients. In general, no age limit for the development of CP is observed. The age range at our centre is 14 months to 99 years, with a mean ± SD age of 61 ± 18 years. Men and women are almost equally affected (women: 55.9%). Patients with CP of varying origins (Fig. 1) are referred to us by dermatologists, GPs, neurologists, gynaecologists, paediatricians. This includes patients with pre-diagnosed dermatosis if the pruritus cannot be controlled; otherwise, dermatologists in private practice typically treat these patients.

There is no uniform clinical phenotype for CP. Patients with CP may present with normal skin, dermatoses, scratch-related skin lesions, or a combination of the last 2 symptoms (Table I). According to the pruritus classification (4), patients can be grouped clinically into 3 groups (Table I). This new classification system has some limitations (Table I), however, apart from this; it is helpful for making decisions about the necessary diagnostic steps and provides a rapid approach for patient assessment independent of CP history.

If CP occurs on skin that appears normal, there is no objective clinical criterion to establish the presence of CP. Furthermore, a validated biomarker for CP diagnosis does not exist; assessment of the symptom is currently based solely on subjective PRO. Typically, intensity of pruritus (e.g. measured on a visual analogue scale; VAS) and QoL are used to determine the course of CP (6, 8, 13). We regularly collect data on these 2 parameters and have demonstrated a high correlation between QoL and itch intensity in CP patients (25). This finding allows for the use of either pruritus intensity or QoL in the clinical assessment of the CP course in the patients showing normal skin. In other patients, the healing of scratch lesions is a sign of relief of pruritus and can serve as clinical marker for the CP course. This is especially helpful in prurigo nodularis. Using an effective antipruritic therapy, prurigo nodules heal subsequently. However, the therapy in prurigo nodularis is extremely challenging and a step-wise therapeutic approach is mandatory (Fig. 2). Novel therapies are urgently needed for patients with prurigo nodularis. In neuropathic pruritus and other types of chronic pruritus, similar approaches and substances, such as, for example, anticonvulsants are recommended by the European guideline (18).

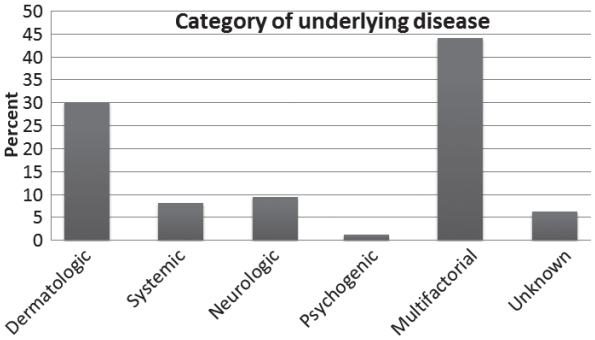

Fig. 1. Classification of patients (analysed in $n = 3{,}116$). The diseases underlying chronic pruritus (CP) can be classified into 6 categories. The most frequent categories at our centre are multifactorial aetiologies ($n = 1{,}378$) and dermatological ($n = 944$) and neuropathic diseases ($n = 295$). Only 195 patients have pruritus of unknown origin (PUO).

MAIN INSIGHTS OBTAINED AND CONSEQUENCES FOR CLINICAL AND BASIC RESEARCH

Gender- and sex-associated factors in chronic pruritus

Although sex and gender are increasingly perceived as important factors in medicine (26, 27), these factors have been neglected in CP patients. We were the first to report on gender-related differences in 1,037 CP patients in several parameters including itch intensity, QoL and scratching behaviour being more severe in women (16). Interestingly, the clinical findings were in alignment with experimental results using fMRI. In a pilot study (28), significant sex-related differences in the central perception and modulation of itch were observed. On the psychophysical level, females demonstrated increased itch intensity and a greater desire to scratch than males. Distraction reduced the itch intensity more efficiently in the lower legs of women and the forearms of men. Using brain imaging, increased activation of the structures responsible for integrating sensory and affective information (e.g. thalamus, precentral gyrus) and motor planning (e.g. cerebellum) was observed in women compared with men.

These findings are highly relevant to clinical studies and basic research. Differences in the symptom's impact on itch intensity and QoL have been detected in women compared with men, thereby leading to different values in PRO and thereby confound outcomes in basic and clinical research. Accordingly, the patient populations included in clinical studies should be carefully selected and data obtained from clinical trials should always also be analysed separately for men and women. Further

Table I. *Presentation of clinical groups in our centre and limitations of the classification*

Clinical group	Patients from our centre, %	Definition	Scratch lesions	Limitations of the group definitions
Chronic pruritus (CP) on inflamed skin	25.4 (n = 801/3,155)	Any dermatosis related to CP	Superimposed (acute) scratch lesions may be present	Dry skin: typically no inflammation; Cutaneous lymphoma: a neoplastic condition
CP on non-inflamed skin	45.8 (n = 1,444/3,155)	No skin lesions visible	Acute scratch lesions may be present	"Invisible" dermatoses could be missed
CP with chronic scratch lesions	28.8 (n = 910/3,155)	Scratch lesions are dominant over an dermatosis or normal skin, e.g. prurigo nodularis, lichen simplex, lichen amyloidosis	Chronic scratch lesions are present: papules, nodules, lichenification	Dermatoses which mimic (chronic) scratch-lesions may be missed: Hypertrophic lichen planus mimics lichen simplex Pruriginous bullous pemphigoid mimics prurigo nodularis Duhring's disease mimics papular prurigo Diagnosis made by histology

research is needed to achieve gender-specific and gender-adapted recommendations for clinical trials and basic research as well as CP diagnostics and treatment.

Explaining clinical observations: relief of itch during distraction

Many patients report reduced pruritus intensity during distraction and increased intensity during rest, anxiety or stress (29–32). Therefore, the psychosomatic consultation is an integral part at our centre. For each individual case, the relevance of organic and psychosomatic factors and their interaction in CP development, maintenance and scratching behaviour are evaluated in 1–3 50-min clinical interviews (9). However, the central representation of relief of itch during distraction was only recently addressed (34, 35). For pain, profound interactions of the central pain-encoding and pain-inhibiting areas (36–41) are well known. We performed a pilot study with 33 healthy volunteers (Stumpf et al., unpublished). During histamine itch stimulation via microdialysis fibres', participants were asked to rate their itch intensity and desire to scratch on the NRS with and without a distraction paradigm (Stroop Task). Interestingly, a sufficient itch reduction was established only when the pure itch sensation was followed by the distraction paradigm. We observed a brainstem activation pattern that is also known to play a role in pain modulation. In conclusion, itch and pain seem to be modulated by overlapping brain regions during distraction.

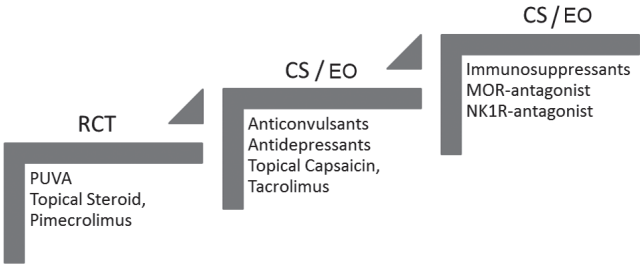

Fig. 2. Therapeutic ladder in prurigo nodularis. In the first step, therapies which have shown a benefit in randomized controlled trials (RCT) are applied. This comprises psoralen plus ultraviolet A (PUVA), topical steroids or topical pimecrolimus (ref. 33). In both next steps, the level of evidence is at case series (CS) and expert opinions (EO). In the second step, substances such as gabapentin, pregabalin and paroxetine are used in our centre which displayed few side effects when used in appropriate dosages. In the third step, cyclosporine and methotrexate can be used as immunosuppressant drugs in a subset of patients which are of general good health. Naltrexone as a mu-opioid receptor (MOR)-antagonist may produce a high number of side-effects and is not effective in all patients. The neurokinin 1 receptor (NK1R) antagonist aprepitant is highly effective, but its use is limited to a small number of patients because of high therapy costs.

FUTURE DIRECTIONS

Searching for new borders in diagnostics: methodological tools to characterize CP

Pruritus and pain share some common pathways in the peripheral and central nervous systems (42–44). Cutaneous nerve fibres and their receptors involved in CP and chronic pain transmission overlap substantially, but are also involved in separate pathways (45, 46). This raises the possibility that sensory abnormalities of CP patients can be detected by devices developed for pain assessment (47). The sensory profile of pain states is assessed by quantitative sensory testing (QST), a standardized method that detects skin sensory abnormalities (47–50). QST is a test battery using different devices to apply different stimuli to the skin in order to detect the threshold for cold, warm and mechanical detection and the corresponding pain detection thresholds. Currently, we have QST data on more than 100 CP patients of different origins (unpublished). For example, we found that loss of sensory function is related to temperature in BRP patients, indicating small fibre function deficits; this observation correlates well with a positive clinical ice pack sign describing BRP only relieved with very cold temperatures (51). Using the QST and clinical data, our aim is to identify patient subgroups that share somatosensory pathology, thereby aiding in the understanding of the itch mechanisms in CP patients and the development of specific treatments.

To better understand the mechanisms underlying CP, we use also other methodological techniques. For example, the determination of intraepidermal nerve fibre density (IENFD) in skin punch biopsies is a method routinely applied for diagnostic purposes in our centre (52). As shown recently, lesional and non-lesional prurigo nodularis (PN) skin biopsies displayed significantly reduced IENFD regardless of clinical parameters suggesting a subclinical small-fibre neuropathy in PN patients (53). Interestingly, we observed dermal hyperplasia of substance P (SP)-positive dermal nerves in PN (54). Thus, we speculate that epidermal hypoplasia and dermal hyperplasia of sensory neurons contributes to peripheral sensitization and maintenance of pruritus in PN (55).

Translational research: a promising route to identify new mechanisms

Finally, we have an ongoing interest in determining the role of certain cutaneous receptors, neuropeptides and neurotransmitters. Our data suggest that molecular and structural alterations in the cutaneous neuroanatomy are relevant for CP and may serve as potential targets for future therapies. For example, an increase in epidermal transient receptor potential vanilloid 1 (TRPV1) is observed in PN, indicating that this receptor has a role in pruritus in PN (56). TRPV1 may be indicated as a therapeutic target as demonstrated in an observational study (57). The hyperplasticity of SP-positive dermal nerves in PN (53) offers an additional target for an antipruritic therapy. SP is a neuropeptide and a mediator of inflammation and pruritus in several diseases, including atopic dermatitis (58). Thus, we were among the first to use an oral antagonist of neurokinin-1 receptor, the SP receptor, in CP patients (59). The results were very impressive and reproducible. To date, more than 100 patients from 7 international groups have been successfully treated with aprepitant, the neurokinin-1 receptor antagonist. We have recently initiated a randomized controlled trial with aprepitant in one of the most promising indications.

Numerous questions remain unanswered regarding mechanisms in CP. These questions demand exploration using a broad-based research approach that bridges clinical and experimental research to promote translational approaches and clinical trials. The fact that numerous patients benefit from our system of medical care (60) encourages us to continue pursuing our aims along the current route.

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The authors declare no conflicts of interest.

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