Acta Derm Venereol 2011; 91: 698–703

CLINICAL REPORT

# Lactase Deficiency: A Potential Novel Aetiological Factor in Chronic Pruritus of Unknown Origin

Sonja A. GRUNDMANN, Ewelina STRATMANN, Randolf BREHLER, Thomas A. LUGER and Sonja STÄNDER
*Department of Dermatology and Competence Center Chronic Pruritus, University Hospital, Münster, Germany*

**Chronic pruritus, which is associated with a wide variety of underlying diseases, represents a challenge in diagnostics and treatment in dermatology and general medicine. The cause of pruritus remains unknown in up to 45% of patients. In this study, 718 patients with chronic pruritus were analysed concerning lactase deficiency, demographic data, aetiology, duration and intensity of pruritus. A total of 154 patients were tested positive for lactase deficiency and 38.3% showed a significant anti-pruritic response to a lactose-free diet (minimum 4 weeks). The best results were observed in patients with pruritus of mixed or unknown origin (*n* = 91; 64% response). Age, sex, localization or duration had no significant influence on the anti-pruritic effect of a lactose-free diet. Lactase deficiency might be an independent causal factor in the elicitation of chronic pruritus. Thus, screening for lactase deficiency represents a rational step in the diagnostic work-up of chronic pruritus. In case of a positive test result, a lactose-free diet offers a low-cost, efficient and specific therapy in patients with chronic pruritus.** ***Key words: itch; lactose intolerance; lactose malabsorption; diet.***

(Accepted February 25, 2011.)

Acta Derm Venereol 2011; 91: 698–703.

Sonja Alexandra Grundmann, Competence Center Pruritus, Department of Dermatology, University of Münster, Von-Esmarch-Strasse 58, DE-48149 Münster, Germany. E-mail: sonja.grundmann@ukmuenster.de

Pruritus is one of the most common symptoms that constitutes a challenge in diagnostics and therapy in dermatology and general medicine, since it is associated with a wide variety of underlying diseases (1). As its intensity is often high, chronic pruritus (over 6 weeks' duration) has a relevant impact on patients' quality of life, affecting their daily activities and sleep (2, 3). In addition to dermatological diseases, the symptom may also have its origin in a variety of systemic, neurological as well as psychogenic disorders (4–8). In up to 45% of cases, the underlying origin remains unknown (pruritus of undetermined origin; PUO) (9, 10). Subclinical or subsided diseases are common reasons for PUO. In addition, an association of as-yet unrelated diseases with pruritic conditions has to be considered. Treudler et al. (11) reported concomitant familial lactose intolerance in a family with chronic aquagenic pruritus. Another group reported a beneficial effect of a lactose-free diet on cutaneous symptoms in patients with lactose intolerance (12, 13). These reports suggest a possible role of lactase deficiency as a causative agent in patients with chronic pruritus.

Lactose intolerance is an important clinical syndrome with a high prevalence worldwide (approximately 70%); the estimated prevalence in Germany and Central Europe ranges from 15% to 20%, whereas in the USA prevalences of 15% among Caucasians, 53% among Mexican-Americans, and up to 80% in the black population are observed (14–16). Lactose intolerance presents with gastrointestinal symptoms, such as diarrhoea or abdominal pain after ingestion and malabsorption of lactose. Lactose malabsorption occurs because of a decreased ability to digest lactose, due to a deficiency in the synthesis of sufficient amounts of the jejunal brush border enzyme lactase-phlorizin hydrolase (LPH) (17). As many variables determine whether a person who malabsorbs lactose develops symptoms, not every individual with lactase deficiency will display gastrointestinal symptoms.

As yet, no studies have addressed a possible association of chronic pruritus and lactase deficiency. The aim of this study was to evaluate the prevalence of lactase deficiency in a random consecutive cohort of patients with severe chronic pruritus and to test the anti-pruritic effect of a lactose-free diet on those identified as having concomitant lactase deficiency.

## PATIENTS AND METHODS

Patients who were referred to our department with chronic pruritus were included in the study (enrolment period 24 months). Chronic pruritus was defined as pruritus lasting longer than 6 weeks of any itch intensity and any origin, except for known and apparent primary skin diseases. All patients were examined according to the current guidelines using clinical and laboratory measures for any underlying diseases causing pruritus (4, 18). Pruritus-specific parameters, such as localization, intensity or quality of the symptom, were obtained through an itch questionnaire (19). According to the position paper of the International Forum for the Study of Itch (IFSI), patients were classified according to the underlying origin of pruritus (dermatological, systemic, neurological, psychogenic, mixed, undetermined) (18). All patients were tested for lactase deficiency by measuring breath hydrogen ($H_2$-exhalation test) based on the hydrogen

value of unabsorbed lactose (50 g lactose, up to 3 h, increase >20 ppm was considered positive) (20). All patients with lactase deficiency were routinely advised by a nutrition expert to follow a lactose-free diet (minimum dietary period of 4 weeks) and to avoid specific anti-pruritic therapy, except for skin moisturizers, in order to ascertain positive dietary effects.

The average intensity of pruritus was evaluated using an 11-point numeric rating scale (NRS-11) before and after the diet. An improvement of ≥4 points in pruritus intensity was defined as a good therapeutic effect (success of lactose-free diet). Patients with lactase deficiency were followed-up (clinical, telephone follow-up) for at least 3 months (up to 27 months) to be included in statistical analysis.

The study received approval from the local ethics committee (Ärztekammer Westfalen-Lippe and Medical Faculty, University of Münster) and patients gave written informed consent for clinical data collection and analysis.

### *Statistical analysis*

Data were collected using Microsoft® Excel (Version 2003, Microsoft, Redmond, WA, USA). Statistical analysis was performed with the SPSS® software package for Microsoft® Windows (German Version 17.0, SPSS Inc., Chicago, IL, USA). Demographic data (age, gender), pruritus intensity on the NRS before and after diet (a reduction in NRS score reflects the efficacy of the lactose-free diet), and the duration of chronic pruritus were given as percentages, mean and standard deviation (SD) of the mean, or as median and range. To detect differences in success of categorized groups, depending on sample size, Fisher's exact or $\chi^2$ test was applied and $p < 0.05$ was considered statistically significant. A Wilcoxon test was performed for the comparison of initial and end-point pruritus intensity ($p < 0.001$ was considered statistically significant).

## RESULTS

### *Total cohort*

A total of 718 patients (307 males (42.8%); 411 females (57.2%) ) with a mean age of 60.8 ± 16.1 years (age range 17–93 years) were enrolled in the study. In 187 patients (26.0%; 58.5 ± 17.0 years) an as-yet unidentified skin disease was found to be the underlying cause of chronic pruritus in 187 patients (26.0%; mean age 58.5 ± 17.0 years), including 36 (5.1%) patients with atopic dermatitis/atopic predisposition. A systemic origin of pruritus was determined in 106 (14.8%; 66.8 ± 12.5 years) patients, whereas 50 (7.0%; 60.5 ± 13.7 years) patients had an underlying neurological disease, and 37 (5.2%; 51.9 ± 16.4 years) a relevant psychogenic disorder. The majority of systemic diseases (77/106, 72.6%) could be observed in elderly patients (>60 years of age). Due to several possible causative factors, 139 (19.4%; 65.7 ± 13.9 years) patients were classified in the group of mixed origin. In 199 patients (27.7%; 58.1 ± 17.0 years), no underlying origin of chronic pruritus could be determined (PUO). The majority of patients reported generalized pruritus (79.1%), whereas 150 patients (20.9%) had localized forms (Fig. 1). The rates of localized and generalized pruritus varied significantly ($p < 0.05$) among the different origins of pruritus (Fig. 1). Pruritus of systemic origin presented as generalized pruritus, whereas neurological disorders preferentially presented as localized forms, most likely due to nerve compressions or focal central nervous system (CNS) disorders.

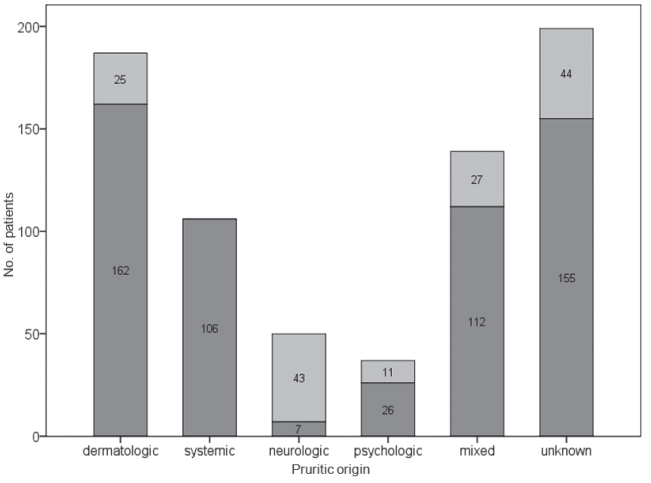


*Fig. 1.* Underlying origin and distribution of chronic pruritus ($n = 718$). *Light grey*: localized pruritus; *dark grey*: generalized pruritus.

### *Patients with lactase deficiency*

In the total cohort of patients, lactase deficiency was diagnosed in 172 patients (24.0%). Prevalence of lactase deficiency in relation to pruritus origin ranged: 16% in neurologic, 18.9% in psychogenic, 19% in dermatologic, 21.7% in systemic, 25.6% in "unknown", and 33.8% in pruritus of mixed origin. Compared with the entire study population, there was no significant difference in age or gender distribution in the group of patients with lactase deficiency (71 males (41%), 102 females (59%); mean age 60.3 ± 16.6, age range 23–88 years). The symptom was of a median intensity of 9 points on the NRS. In those patients with chronic pruritus and concomitant lactase deficiency, the median duration of pruritus was 36 months (2–576, mean 67.3 ± 89.1). Along with the long duration, pruritus was found to be refractory to at least one therapeutic attempt.

### *Effect of a lactose-free diet*

Eight out of 172 patients (4.6%) followed no diet, 10 patients (5.8%) were lost to follow-up. Thus, the anti-pruritic effect of a lactose-free diet was analysed in a population of 154 patients (65 males (42%), 89 females (58%); mean age 60.6 ± 16.5 years; median age 63.5 years; age range 23–88 years; median duration of pruritus 36 months (2–576), mean 68.2 ± 92.4) with lactase deficiency and chronic pruritus. A lactose-free diet for at least 4 weeks had a beneficial therapeutic effect (pruritus score improvement ≥4 point) in 59

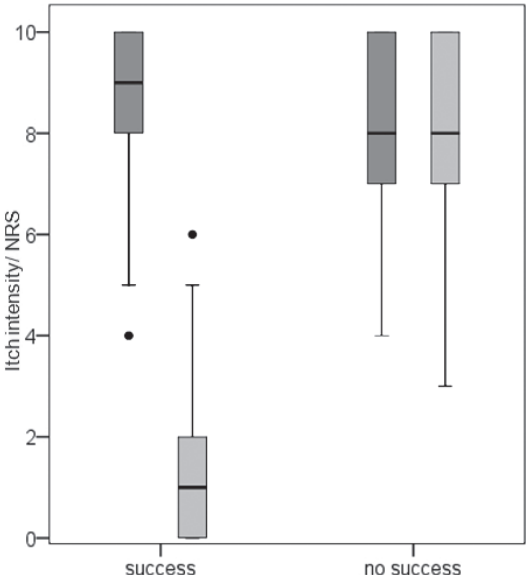


*Fig. 2.* Initial and end-point pruritus intensity in patients with lactase deficiency ($n = 154$). *Dark grey*: initial itch intensity, *light grey*: end-point itch intensity, success was defined as improvement of ≥4 points in pruritus intensity.

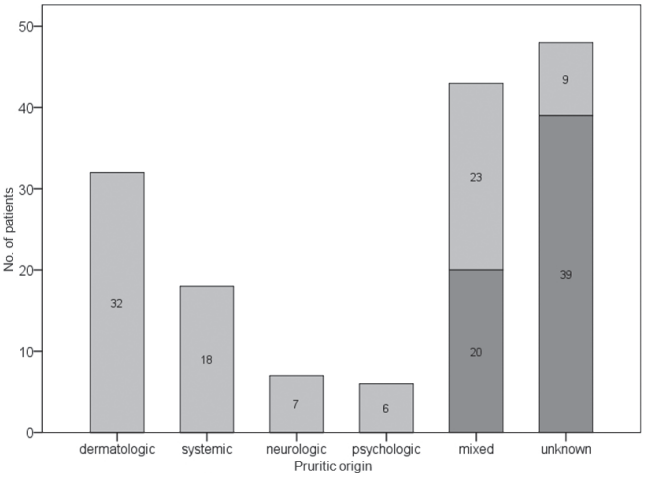


*Fig. 3.* Pruritic aetiology and benefit of a lactose-free diet in patients with lactase deficiency ($n = 154$). *Light grey*: no success; *dark grey*: success.

(38.3%) of the 154 patients. Patients who responded had a significant difference in NRS reduction compared with non-responders ($p < 0.001$, Fig. 2). Initial median pruritus intensity was NRS 9 (4–10), whereas median NRS after lactose-free diet was 1 (0–6). Thus, the median improvement in pruritus intensity was 8 (4–10) in patients on a lactose-free diet. In the long-term, some patients reported immediate recurrence of pruritus with dietary non-compliance.

All patients responding to the diet belonged to the group with mixed (20/59; 33.9%) or unknown (39/59; 66.1%) aetiology of chronic pruritus (Fig. 3). Thus, 64.8% of patients with mixed pruritus or pruritus of unknown aetiology (59/91 patients, $p < 0.05$) derived significant clinical benefit from the diet. The localization (generalized or localized pruritus, $p = 0.70$), or duration of pruritus ($p = 0.19$, Table I), as well as age distribution of patients ($p = 0.75$, Table II) did not differ significantly among responders and non-responders.

Independent of pruritus origin, females with lactase deficiency and chronic pruritus benefited slightly more from a lactose-free diet (39/89 females, 43.8%); this also occurred in females belonging to the subgroup with chronic pruritus of mixed or unknown origin (39/59 females, 66.1%). Three patients with localized pruritus responding to a lactose-free diet were initially suspected to suffer from brachioradial pruritus; however, magnetic resonance imaging (MRI) of the cervical spine revealed no relevant pathologies. In patients complaining of anogenital pruritus ($n = 3$), notalgia paraesthetica ($n = 2$), and one patient with pruritus localized on the torso, MRI imaging did not reveal any underlying nerve compressions. In contrast, MRI examinations revealed significant pathologies (spinal cord compression, neural root compression) in patients with localized pruritus, who did not benefit from a lactose-free diet (4/4 patients with brachioradial pruritus, 2/3 patients with genitoanal pruritus). Of the entire study population, 2.8% (20/718) had aquagenic pruritus of mixed or unknown origin. In 11 patients (55%) concomitant lactase deficiency could be observed and a lactose-free diet had a significant anti-pruritic effect in more than 50% of them (6/11; 54%). Although higher in trend, the response rate in patients with aquagenic pruritus could not be proven to be of higher statistical significance compared with patients with non-aquagenic forms of chronic pruritus (response in 53/143 patients; 37%; $p = 0.25$).

## DISCUSSION

In this study we surveyed the presence of lactase deficiency in a consecutive cohort of patients with chronic pruritus. Lactose intolerance unites a heterogeneous group of patients with primary (genetically) or secondary (acquired) lactase deficiency. For example, genetic factors are known to influence tolerance and

Table I. *Duration of pruritus and benefit of a lactose-free diet in patients with lactase deficiency (*n = *154)*

| | Duration/months | | | | | |
|---|---|---|---|---|---|---|
| | <13 *n* (%) | 13–36 *n* (%) | 37–72 *n* (%) | 73–120 *n* (%) | >120 *n* (%) | Total of patients *n* (%) |
| Benefit | 17 (44.7) | 14 (33.3) | 14 (48.3) | 8 (33.3) | 6 (28.6) | 59 (38.3) |
| No benefit | 21 (55.3) | 28 (66.7) | 15 (51.7) | 16 (66.7) | 15 (71.4) | 95 (61.7) |
| Total | 38 (100) | 42 (100) | 29 (100) | 24 (100) | 21 (100) | 154 (100) |

Table II. *Age-dependent benefit of lactose-free diet in patients with lactase deficiency (*n = *154)*

| | Age/years | | | | | |
|---|---|---|---|---|---|---|
| | <21 *n* (%) | 21–40 *n* (%) | 41–60 *n* (%) | 61–80 *n* (%) | >80 *n* (%) | Total of patients *n* (%) |
| Benefit | 0 (0) | 8 (34.8) | 21 (46.7) | 26 (37.1) | 4 (25) | 59 (38.3) |
| No benefit | 0 (0) | 15 (65.2) | 24 (53.3) | 44 (62.9) | 12 (75) | 95 (61.7) |
| Total | 0 (100) | 23 (100) | 45 (100) | 70 (100) | 16 (100) | 154 (100) |

disease expression in patients with lactase deficiency, as single nucleotide polymorphisms (SNPs) of lactase (LCT)-gene regulatory elements (chromosome 2q21) are associated with primary adult lactose intolerance (21–24). In this study, we did not distinguish between primary and secondary lactase deficiency. However, the history of chronic pruritus in adult patients starting only years before and not in childhood supports secondary lactose intolerance. Genetic evaluations of LCT-gene polymorphisms in patients who respond to a lactose-free diet and those who fail to do so might elucidate a possible association of primary or secondary lactase deficiency with pruritic conditions. Although lactase deficiency is of high prevalence in the general population, the observed response to the appropriate diet suggests no incidental coincidence.

Lactose intolerance usually presents with gastrointestinal symptoms, which are known to be reasonably controlled by a lactose-free diet. However, due to the variety of often mild or vague symptoms, a high number of unreported cases may exist. Among our cohort of 718 patients with chronic pruritus, 24% were identified to have lactase deficiency. Thus, the observed prevalence of lactase deficiency is comparable to, or just slightly higher than, the overall prevalence observed in Germany (15–20%). In our patients, pruritus was supposed to be therapy-refractory and the individual disease burden was high, as reflected by the high intensity of pruritus (median intensity: 9 on the NRS-11) and the long duration (median: 36 months). Of the affected patients 89.5% followed a lactose-free diet for a minimum period of 4 weeks and avoided specific anti-pruritic therapies. Overall, 38% of patients with lactase deficiency showed a significant anti-pruritic response to a lactose-free diet. Especially in patients with chronic severe pruritus of mixed or unknown origin, the observed response rate to dietary intervention was as high as 65%. This was accompanied by a significant improvement in pruritus intensity (median pruritus intensity NRS 9→1). In these patients with PUO, the aetiology of pruritus would have remained undetermined if lactase deficiency had not been taken into consideration. Interestingly, in patients with aquagenic pruritus also, more than 50% of patients derived significant benefit from the diet, suggesting lactose intolerance as a co-factor, as already discussed by Treudler et al. (11). A lactose-free diet had no significant therapeutic effect in patients with pruritus of dermatological, neurological, psychiatric or systemic origin. Age, gender, or duration of the symptom had no significant influence on response to a lactose-free diet, although a trend towards a higher response in females and younger patients, with shorter duration, could be observed.

The high response rates and the significant NRS-reduction indicate a specific therapeutic success. Our results suggest an independent and crucial role of lactose metabolism in the elicitation of chronic pruritus of otherwise unknown origin and seem to justify a dietary therapeutic attempt in patients with chronic pruritus and concomitant lactase deficiency. Furthermore, some patients reported an immediate relapse of pruritus when the dietary recommendation was not adhered to. This emphasizes the role of lactase deficiency as an independent causal factor in pruritus.

The mechanism of lactase deficiency-induced pruritus is currently unknown. In view of the shown therapeutic benefit of a lactose-free diet in our study collective, a pivotal role of lactose metabolism in the pruritic cascade can be assumed.

Besides a possible genetic association, pruritus is known to be a symptom of inflammatory diseases (25). Accordingly, anti-inflammatory drugs affecting inflammatory cascades were found to have beneficial effects on pruritic diseases (26). Lactose intolerance might elicit and maintain chronic pruritus via inflammatory mechanisms. We hypothesize a common intracellular target within the pruritic inflammatory cascade. Structure alignment analysis by NCBI-BLAST, a well-established technique to analyse sequence homologies, showed significant molecular resemblance between lactase-phlorizin hydrolase (LPH) and NF-kappa B repressing factor (NRF) (27, 28). Therefore, NRF might be a key mediator merging both pathways. As well, its ligand, NF-kappa B is thought to be a potent pruritogenic mediator, because its activation is known significantly to reduce scratching behaviour in mice (29). In addition, avenanthramides were shown to have potent anti-inflammatory and anti-pruritic effects by decreased phosphorylation of NF-kappa B (30, 31). Similar to inflammatory conditions, NF-kappa B might be an intracellular key mechanism in pruritus associated with haematological diseases (32). Mutations of the JAK2 cascade are common in these patients, who often complain of aquagenic pruritus (33–35). Experimental data might support a common pathway involving bifunctional NF-kappa B JAK/Stat response elements

(36). Moreover, in infectious diseases, HIV is known to be associated with severe forms of chronic pruritus. A structural resemblance of HIV1-LTR and NRF might be an additional piece of the puzzle to further elucidate intracellular cascades involved in pruritic conditions (37). However, to confirm these data, linking lactose metabolism, inflammatory cascades and pruritus, further experimental data are required. Thus, to promote a specific drug design, it is essential exactly to define the crucial elements involved in lactose intolerance-associated pruritogenesis. The statistical data of this study on a large collective of patients suggest a key role of lactose metabolism in pruritic, and possibly also in a broader range of inflammatory, diseases.

The results of this study suggest that lactase deficiency is an independent causal factor in chronic pruritus. We therefore propose including lactase deficiency tests in the routine clinical work-up of all patients with chronic PUO. Recommending a lactose-free diet to those with confirmed lactase deficiency is a simple, cost-effective, yet specific, therapeutic attempt. The dietary approach is promising given the high response rate observed in this study to a lactose-free diet, even in older patients with severe chronic pruritus of long duration, resulting in a significant improvement in pruritus intensity. Furthermore, in general, no additive therapies were required and dietary compliance, although demanding some effort on the part of patients, was high.

This pilot study has some design limitations. An open, uncontrolled design was used to gather initial information on this novel anti-pruritic concept. Although observational study findings are pragmatic and representative of real-life, further well-controlled, randomized studies are required in order to test and prospectively establish the lactose-free diet as a therapeutic approach in patients with chronic pruritus, including those in whom no reasonable therapeutic options appear to be available.

## ACKNOWLEDGEMENT

We thank M.-L. Siemer for excellent technical assistance with lactose intolerance testing.

## REFERENCES

1. Yosipovitch G, Greaves MW, Schmelz M. Itch. Lancet 2003; 361: 690–694.
2. Sheehan-Dare RA, Henderson MJ, Cotterill JA. Anxiety and depression in patients with chronic urticaria and generalized pruritus. Br J Dermatol 1990; 123: 769–774.
3. Ikoma A, Steinhoff M, Stander S, Yosipovitch G, Schmelz M. The neurobiology of itch. Nat Rev Neurosci 2006; 7: 535–547.
4. Ständer S, Streit M, Darsow U, Niemeier V, Vogelgsang M, Ständer H, et al. Diagnostisches und therapeutisches Vorgehen beichronischem Pruritus. J Dtsch Dermatol Ges 2006; 4: 350–370.
5. Narita I, Iguchi S, Omori K, Gejyo F. Uremic pruritus in chronic hemodialysis patients. J Nephrol 2008; 21: 161–165.
6. Bergasa NV. Update on the treatment of the pruritus of cholestasis. Clin Liver Dis 2008; 12: 219–234.
7. Jones EA, Bergasa NV. The pruritus of cholestasis and the opioid system. JAMA 1992; 268: 3359–3362.
8. Schneider G, Driesch G, Heuft G, Evers S, Luger TA, Ständer S. Psychosomatic cofactors and psychiatric comorbidity in patients with chronic itch. Clin Exp Dermatol 2006; 31: 762–767.
9. Sommer F, Hensen P, Bockenholt B, Metze D, Luger TA, Ständer S. Underlying diseases and co-factors in patients with severe chronic pruritus: a 3-year retrospective study. Acta Derm Venereol 2007; 87: 510–516.
10. Weisshaar E, Dalgard F. Epidemiology of itch: adding to the burden of skin morbidity. Acta Derm Venereol 2009; 89: 339–350.
11. Treudler R, Tebbe B, Steinhoff M, Orfanos CE. Familial aquagenic urticaria associated with familial lactose intolerance. J Am Acad Dermatol 2002; 47: 611–613.
12. Matthews SB, Waud JP, Roberts AG, Campbell AK. Systemic lactose intolerance: a new perspective on an old problem. Postgrad Med J 2005; 81: 167–173.
13. Nenoff P, Domula E, Willing U, Herrmann J. Giardia lamblia – Ursache von Urtikaria und Pruritus oder zufällige Assoziation? Hautarzt 2006; 57: 518–522.
14. Voelker R. NIH panel tackles lactose intolerance. JAMA 2010; 303: 1240–1242.
15. Brannon PM, Carpenter TO, Fernandez JR, Gilsanz V, Gould JB, Hall KE, et al. NIH Consensus Development Conference Statement: Lactose Intolerance and Health. NIH Consens State Sci Statements 2010; 27.
16. Vesa TH, Marteau P, Korpela R. Lactose intolerance. J Am Coll Nutr 2000; 19: 165S–175S.
17. Campbell AK, Waud JP, Matthews SB. The molecular basis of lactose intolerance. Sci Prog 2009; 92: 241–287.
18. Stander S, Weisshaar E, Mettang T, Szepietowski JC, Carstens E, Ikoma A, et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. Acta Derm Venereol 2007; 87: 291–294.
19. Lotts T, Klein D, Chatzigeorgakidis E, Iking A, Phan NQ, Ständer S. Multidimensional database for pruritus patients – statistical evaluation of clinical characteristics Acta Derm Venereol 2009; 89: 691.
20. Beyerlein L, Pohl D, Delco F, Stutz B, Fried M, Tutuian R. Correlation between symptoms developed after the oral ingestion of 50 g lactose and results of hydrogen breath testing for lactose intolerance. Aliment Pharmacol Ther 2008; 27: 659–665.
21. Bodlaj G, Stocher M, Hufnagl P, Hubmann R, Biesenbach G, Stekel H, et al. Genotyping of the lactase-phlorizin hydrolase –13910 polymorphism by LightCycler PCR and implications for the diagnosis of lactose intolerance. Clin Chem 2006; 52: 148–151.
22. Enattah NS, Sahi T, Savilahti E, Terwilliger JD, Peltonen L, Jarvela I. Identification of a variant associated with adult-type hypolactasia. Nat Genet 2002; 30: 233–237.
23. Enattah NS, Trudeau A, Pimenoff V, Maiuri L, Auricchio S, Greco L, et al. Evidence of still-ongoing convergence evolution of the lactase persistence T-13910 alleles in humans. Am J Hum Genet 2007; 81: 615–625.
24. Kuokkanen M, Kokkonen J, Enattah NS, Ylisaukko-Oja T, Komu H, Varilo T, et al. Mutations in the translated region of the lactase gene (LCT) underlie congenital lactase deficiency. Am J Hum Genet 2006; 78: 339–344.
25. Steinhoff M, Bienenstock J, Schmelz M, Maurer M, Wei E, Biro T. Neurophysiological, neuroimmunological,

and neuroendocrine basis of pruritus. J Invest Dermatol 2006;126: 1705–1718.
26. Pogatzki-Zahn E, Marziniak M, Schneider G, Luger TA, Ständer S. Chronic pruritus: targets, mechanisms and future therapies. Drug News Perspect 2008; 21: 541–551.
27. Grundmann SA, Ständer S. Aminosäuresequenzhomologie zum NF-kappa B repressing factor (NKRF): Schlüsselfaktor bei Laktoseintoleranz-vermitteltem Pruritus?. J Dtsch Dermatol Ges 2009; 7: 1015.
28. Bartels M, Schweda AT, Dreikhausen U, Frank R, Resch K, Beil W, et al. Peptide-mediated disruption of NFkappaB/NRF interaction inhibits IL-8 gene activation by IL-1 or Helicobacter pylori. J Immunol 2007; 179: 7605–7613.
29. Han SJ, Ryu SN, Trinh HT, Joh EH, Jang SY, Han MJ, et al. Metabolism of cyanidin-3-O-beta-D-glucoside isolated from black colored rice and its antiscratching behavioral effect in mice. J Food Sci 2009; 74: 253–258.
30. Sur R, Nigam A, Grote D, Liebel F, Southall MD. Avenanthramides, polyphenols from oats, exhibit anti-inflammatory and anti-itch activity. Arch Dermatol Res 2008; 300: 569–574.
31. Sancho R, Calzado MA, Di Marzo V, Appendino G, Munoz E. Anandamide inhibits nuclear factor-kappa B activation through a cannabinoid receptor-independent pathway. Mol Pharmacol 2003; 63: 429–438.
32. Diehn F, Tefferi A. Pruritus in polycythaemia vera: prevalence, laboratory correlates and management. Br J Haematol 2001; 115: 619–621.
33. Spivak JL. Narrative review: thrombocytosis, polycythemia vera, and JAK2 mutations: The phenotypic mimicry of chronic myeloproliferation. Ann Intern Med 2010;152: 300–306.
34. Tefferi A, Gilliland DG. The JAK2V617F tyrosine kinase mutation in myeloproliferative disorders: status report and immediate implications for disease classification and diagnosis. Mayo Clin Proc 2005; 80: 947–958.
35. Vannucchi AM, Antonioli E, Guglielmelli P, Rambaldi A, Barosi G, Marchioli R, et al. Clinical profile of homozygous JAK2 617V>F mutation in patients with polycythemia vera or essential thrombocythemia. Blood 2007; 110: 840–846.
36. Ganster RW, Taylor BS, Shao L, Geller DA. Complex regulation of human inducible nitric oxide synthase gene transcription by Stat 1 and NF-kappa B. Proc Natl Acad Sci USA 2001; 98: 8638–8643.
37. Dreikhausen U, Hiebenthal-Millow K, Bartels M, Resch K, Nourbakhsh M. NF-kappa B-repressing factor inhibits elongation of human immunodeficiency virus type 1 transcription by DRB sensitivity-inducing factor. Mol Cell Biol 2005; 25: 7473–7483.