Pruritus, impaired mental health and inflammation contribute to morbidity in end-stage renal disease. There are no studies on all 3 conditions. We therefore obtained inflammatory parameter data (C-reactive protein and interleukin-6), pruritus data and psychological testing data (36-Item Short-Form Health Survey, “Allgemeine Depressionsskala” and Toronto Alexithymia Scale-20) for 19 dialysis patients with pruritus, 20 dialysis patients without pruritus and 15 healthy controls. Non-parametric hierarchical clustering revealed 3 clusters of parameters: one mainly driven by pruritus scores (chronic kidney disease-associated pruritus cluster), one by mental health scores (mental health cluster) and one by inflammatory parameters (inflammatory cluster). Factor analysis showed strong associations (mental health cluster/chronic kidney disease-associated pruritus cluster, r = -0.49; mental health cluster/inflammatory cluster, r = -0.52; inflammatory cluster/chronic kidney disease-associated pruritus cluster, r = 0.48). For the first time, complete correlations between inflammation, mental health and pruritus in dialysis patients have been established. As all 3 conditions are associated with mortality, knowledge about their interdependence helps to understand end-stage renal disease pathophysiology.

Key words: inflammation; IL-6; pruritus; depression; quality of life (QoL); dialysis.

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Patients with chronic kidney disease (CKD) exhibit many alterations and comorbidities including uremic pruritus (also called CKD-associated pruritus [CKD-aP]), impaired mental health (iMH) and chronically elevated levels of inflammatory parameters (e.g. C-reactive protein [CRP] and interleukin [IL]-6). CKD-aP is associated with reduced quality of life (1) and psychosocial alterations in patients who require renal replacement therapy (RRT) (2). Based on several observations and results from various trials on CKD-aP, there is evidence that CKD-aP is a systemic disease rather than an isolated skin disease (3). The involvement of alterations of the immune system and a pro-inflammatory pattern (pIP) in the pathogenesis of CKD-aP has been discussed in the past, but remains still unclear (3, 4). This was noted as one of the most important fields of research in CKD (5).

Additionally, the prevalence of iMH is high among patients with end-stage renal disease (ESRD) (6). It has been shown that iMH can also affect somatic outcomes (7). Of note, pIP – and especially elevation of IL-6 – was recently reported to be involved in the development of depression and other iMH conditions (8). Furthermore, pIP may be a major contributor to morbidity and mortality in ESRD (9).

Based on this, it can be assumed that a correlation exists at least between one pair of these factors (CKD-aP, pIP and iMH). However, a simultaneous analysis and characterization of the correlations between all 3 factors is still missing. Gaining knowledge about the interdependence of these factors may help to understand the pathophysiological mechanisms underlying all 3 aspects of morbidity in ESRD.

SIGNIFICANCE

Itch, impaired mental health and inflammation contribute to morbidity in dialysis patients. We therefore analysed laboratory results, intensity of itch and psychological tests in dialysis patients with pruritus, without and healthy people. The data was analysed by different statistical tests. This revealed 3 independent groups. One was mainly driven by itch, one by mental health and another by inflammatory parameters. Additionally, all 3 showed strong associations. This means inflammation, mental health and itch are somehow interconnected in dialysis patients. Since all 3 comorbidities are associated with the risk of death, knowledge about the interdependence of these factors is important.

METHODS

Patients and controls

Data on hemodialysis (HD) patients (with and without CKD-aP) and controls, including inflammatory parameter data, were previously published (4). In this study, we included further data regarding 13 patients who were undergoing peritoneal dialysis (PD), and data on psychological test results, where available. This data-enriched post-hoc analysis therefore included 19 dialysis (RRT) patients with CKD-aP (“RRT-CKD-aP” subgroup: 6 PD patients and 13 HD patients) and 20 age-matched dialysis (RRT)
patients without pruritus (“RRT” subgroup: 7 PD patients and 13 HD patients). Another control group consisted of 15 healthy individuals (“control” subgroup), as confirmed by clinical history and basic laboratory parameters. Patients in the RRT-CKD-aP subgroup were included if they experienced substantial pruritus for ≥ 3 months (10). Substantial CKD-aP was defined as a visual analogue scale (VAS) score ≥ 3 (0 = no pruritus to 10 = unbearable pruritus). Furthermore, patients in both dialysis groups had to be on RRT for ≥ 6 months and had to be well dialyzed, with a Kt/V ≥ 1.3 in HD patients and ≥ 2.1 (weekly) in PD patients at the time of laboratory testing.

A full data set of every variable in this retrospective analysis was available for 39 of the 54 individuals. Regarding the 9 variables included in the factor and clustering analyses, 40 of the 54 patients had complete data (with incomplete psychological data for the remaining 14 patients).

**Exclusion criteria**

Patients with infection, other active inflammatory disease, a history of skin diseases, liver disease, and systemic diseases such as malignancy and allergic diathesis, and patients on immunosuppressive therapy, were excluded.

**Pruritus assessments**

For screening, the dialysis patients were asked to estimate their itching intensity by marking a VAS (0 = no pruritus to 10 = unbearable pruritus). CKD-aP was assessed using the VAS during a 7-day period (marked daily in the week during which the blood samples were obtained) and the median value was calculated. Furthermore, patients in both dialysis groups had to be on RRT for ≥ 6 months and had to be well dialyzed, with a Kt/V ≥ 1.3 in HD patients and ≥ 2.1 (weekly) in PD patients at the time of laboratory testing.

**Mental health assessments**

Three tools were used to assess iMH: The Depression Scale (‘‘Allgemeine Depressionsskala – Langform’’ [ADS-L]), the 36-Item Short-Form Health Survey (SF36) quality of life scale and the Toronto Alexithymia Scale 20 (tas-20), all validated in German. A full data set of psychological test results was obtained for 15 patients in the RRT group, 11 in the RRT-CKD-aP group and 14 in the control group. These parameters are regarded as iMH parameters throughout this paper.

**Laboratory investigations**

In all HD patients, blood samples were obtained after a long dialysis-free weekend before starting HD. In the healthy control group and PD patients, blood was drawn after taking the subject’s medical history and conducting a short physical examination. Samples were processed within 2 h of collection.

The following parameters were measured automatically in our routine clinical laboratory: leukocytes (g/l), hemoglobin (g/l), hematocrit (%), platelets (g/l), ferritin (µg/l), transferrin (mg/dl), albumin (g/dl), total protein (g/dl), creatinine (mg/dl), urea (mg/dl), glucose (mg/dl), sodium (mmol/l), potassium (mmol/l), calcium (mmol/l), phosphate (mmol/l), parathyroid hormone (PTH) (pmol/l), alkaline aminotransferase (ALT) (U/l), aspartate aminotransferase (AST) (U/l), alkaline phosphatase (AP) (mg/dl), gamma-glutamyl transferase (GGT) (mg/dl), CRP (mg/dl) and IL-6 (pg/ml). CRP was measured to the nearest 0.1 mg/dl. For data management purposes, values < 0.5 mg/dl were set to 0.4 mg/dl. The laboratory assessments for each participant followed a previously published protocol (4). CRP and IL-6 are regarded as inflammatory parameters throughout this paper.

**Statistical analysis**

Kruskal–Wallis and Wilcoxon rank-sum tests were employed to compare medians between groups. To test correlations, Spearman’s rho statistic was used.

In the non-parametric hierarchical clustering analysis, the homogeneity measure was based on the Pearson correlation. Initially, most similar variables were paired into (basic) clusters. These clusters were then repeatedly merged until a root cluster contained all variables.

In the exploratory factor analysis, we used an oblique factor rotation method for modeling correlated factors. To decide on the number of factors in our model, we used the chi-square statistic. To ensure a clear graphical depiction of the factor model, no arrows with factor loadings with absolute values < 1/3 are shown. Missing values were imputed using random forests (17). Findings were considered to be significant if p-values were < 0.05. Statistical analysis was performed with R (18), version 3.4.2, using the packages ClustOfVar (19) for clustering variables, Hmisc (20) for plotting correlation matrices, psych (21) for factor analysis, randomForestSRC (22) for imputation of missing values and qgraph (23) for displaying networks.

**RESULTS**

**Patient characteristics**

Causes of ESRD were equally distributed between those with pruritus (RRT-CKD-aP group) and those without (RRT group) (Table I). The controls had a younger median age (52 in the control group vs. 64 in both dialysis groups). Kruskal–Wallis and Wilcoxon rank-sum tests performed for all parameters revealed significantly altered values in the dialysis groups compared to the healthy controls regarding the mental health scores tas-20 and ADS-L (see Table I), inflammatory parameters (CRP and IL-6), hemoglobin, ferritin, transferrin, phosphate and PTH levels (see Table I).
In pruritus patients (RRT-CKD-aP group), the medians of AP, CRP and IL-6 were significantly different to levels in the pruritus-free dialysis group (RRT group). Thus, these parameters were included in the further analyses. Of note, indicators of other diseases associated with pruritus (ALT, AST, GGT, PTH, phosphate transferrin and ferritin levels) did not differ significantly between pruritus-free dialysis and RRT groups (for numbers, see Table I), although there was a non-significant trend of increased PTH levels in the pruritus patients.

Parameter correlations

Parameter correlations were found between all variables, apart from AP, which was the only parameter not significantly correlated with the psychological parameters SF36-msc, ADS-L and tas-20 (Table II).

Correlations were, as expected, strongest within each group of associated measurements: mental health parameters, pruritus parameters and inflammatory parameters (mental health: SF36-msc with tas-20, r=−0.70; SF36-msc with ADS-L, r=−0.69; ADS–L with tas-20, r=0.66; pruritus parameters: VAS with Duo, r=0.98; inflammatory parameters: CRP with IL-6, r=0.79) (see Table II). Of note, SF36-psc deviated from this pattern and was most strongly correlated with IL-6 (r=−0.73) and the two pruritus parameters (r=−0.61 and −0.6) (also see Table II). Additionally, AP was most strongly correlated with the two pruritus parameters (both r=0.49).

Regarding cross-group correlations involving the 4 mental health parameters, they were all most strongly correlated with IL-6 (r range = −0.38 to −0.73; also see Table II). Regarding cross-group correlations involving the two inflammatory parameters, they were both most strongly correlated with S36-psc (r=−0.55 and −0.73 respectively; also see Table II) followed by the two pruritus parameters (r range = 0.48 to 0.58; also see Table II).

Non-parametric hierarchical clustering

To measure the heterogeneity within a cluster, the y-axis value (height) is used. For example, the VAS and Duo
variables are much more homogeneous than for example
ADS-L and SF36-msc (Fig. S1). On the basic level, clusters consisted of pairs of variables that were more similar to each other than to any other variable. On the intermediate level, non-parametric hierarchical clustering of the observed variables revealed 3 clusters. Based on the dominant parameters, we designated the clusters the inflammatory cluster (I-C: log(CRP), log(IL-6) and additionally SF36-psc), the mental health cluster (MH-C: tas-20, SF36-msc and ADS-L) and the chronic kidney disease-associated pruritus cluster (CKD-aP-C: VAS, Duo and additionally log(AP)). Each of these clusters contained variables that were more similar to the variables within the cluster and more dissimilar to the variables outside the cluster. Overall, these 3 clusters formed the most homogenous clusters of any combination of clusters of the intermediate level. These findings are in perfect accordance with the results of the factor analysis discussed in the following section.

**Factor analysis**

All 9 single parameters were included in the exploratory factor analysis, along with 3 latent factors. Tests with only two factors were insufficient (p < 0.001, chi-square statistic = 45.06, df = 19) and adding a fourth factor did not provide substantial additional informational content (p = 0.78, chi-square statistic = 8.02, df = 12). The three-factor model was able to explain 65.7% of the variance in the data set.

Factor 1 of the model was highly loaded by the pruritus parameters (compare this with the CKD-aP-C hierarchical cluster) (loadings: VAS = 0.91 and Duo = 1) and to a lesser extent, AP (loading: log(AP) = 0.52), which was also a CKD-aP-C cluster variable. Factor 2 was mainly driven by the mental health variables (compare this with the MH-C hierarchical cluster) (loadings: tas-20 = 0.82, ADS-L = 0.77, SF36-msc = –0.84). Factor 3 was highly loaded by the inflammatory variables CRP and IL-6 (compare this with the I-C hierarchical cluster) (loadings: log(IL-6) = 0.96 and log(CRP) = 0.72) and to a lesser extent, SF36-psc (loading = –0.42) (Fig. S2).

As these results are in perfect accordance with the 3 hierarchical clusters from the analysis above, we propose that Factor 1 mainly reflects pruritus, Factor 2 represents mental health and Factor 3 represents inflammation.

Of note, the exploratory factor analysis revealed pairwise associations between each of the established factors/clusters of the model (CKD-aP-C with MH-C, r=0.49; CKD-aP-C with I-C, r=0.48; MH-C with I-C, r=0.52, see the correlation structure of the factors in Fig. S2).
of the 3 aspects of morbidity when analyzed together. We were able to establish a factor model involving diverse parameters that consistently formed clusters with high degrees of association, which resemble a pruritus cluster, an iMH and quality of life cluster and an inflammation cluster. In this model, higher inflammatory parameters were associated with worse iMH and pruritus symptoms, while worse pruritus symptoms were associated with worse iMH in dialysis patients. This adds to the growing body of evidence on the complex nature of morbidity in ESRD that is most probably of multifactorial origin.

As AP level was the only parameter that was significantly elevated in dialysis patients with pruritus compared to dialysis patients without pruritus, we included this parameter in our analysis. AP was most strongly correlated with the two pruritus parameters, an association so far undescribed in the literature. Of note, dialysis patients with pruritus did not have any signs of liver impairment (normal levels for GGT, AST and ALT) or high bone turnover (PTH levels did not significantly differ from those in the dialysis patients without pruritus, and they were within desired ranges for dialysis patients), although there was a non-significant trend towards increased PTH levels in pruritus patients. One limitation of the study is that AP was not differentiated by its origin. For example, in addition to the mostly well-known bone and biliary AP, there is also an intestinal AP that might have contributed to increased AP levels (33), with the potential role of nutrition as a confounding factor (34). Further studies can shed more light on the role of AP in pruritus.

Further, systematic bias in patient selection may have occurred (based on subjective, self-reported pruritus) and bias may also have occurred due to social desirability in the answers to questions used for data collection (including mental health questions). On the other hand, different standard psychological questionnaires were included, and they showed a high level of consistency, underlining the inter-test reliability and overall reliability of the mental health assessments. Furthermore, VAS for pruritus assessment is considered an appropriate and validated tool for the assessment of pruritus (35). Of note, the analysis showed a very high correlation between the VAS and Duo scores (r=0.98) – this indicates that there is no additive value of the Duo score and the simple VAS seems to be sufficient to test for uremic pruritus. Of course, the small sample size further limits interpretation. However, we did find highly significant results despite the small sample size, emphasizing the robustness of our findings.

It seems feasible to overcome the restrictions of pairwise analyses, which led to contradictory and heterogeneous results in the past, by using statistical models such as non-parametric cluster analyses on larger cohorts to validate our findings for a better understanding of cross-group interactions.

Due to the nature of our study, conclusions regarding causality cannot be drawn. However, the existence of causal associations is supported by recent observation regarding the inflammation lowering effects of anti-depressive treatments (36, 37). Yet, it remains unclear whether this is a mere pleiotropic side effect of anti-depressive medication, one of multiple modes of action of this medication or the result of an improved mental health status. Therefore, further investigations on the effects of treatment options for one condition on the severity of the other conditions, especially in CKD patients, are needed to assert possible causality.

Interestingly, a currently published observational study in a large, representative cohort in Germany (GEHIS cohort) was also focused on quality of life and mental health in pruritus patients on dialysis (1, 38, 39). This study found significant associations between pruritus severity and the 12-Item Short Form Health Survey (SF-12) and the Hospital Anxiety and Depression Scale (HADS) (1), but no significant associations between pruritus severity and laboratory parameters (39).

Other research focusing on CKD-aP and inflammation found associations supporting an involvement of pILP (30). Regarding the association between pILP and iMH, meta-analyses on the association between serum inflammatory markers (foremost, IL-6 and CRP) and depression showed positive associations in previous population-based studies (40, 41). Based on these observations in the general population, previous studies in patients with ESRD showed heterogeneous results (c.f. 42, 43).

Conclusion

Our results show that pIP, CKD-aP and iMH are contributors to ESRD-related morbidity. These 3 health conditions are moderately associated with each other while being defined by distinct parameters. These findings might influence the way we perceive different aspects of morbidity in RRT patients, which have been reviewed and investigated as separate entities in the past. We want to emphasize that we face a complex system of symptoms and conditions in dialysis patients and one should be aware that mutual influences between the different aspects of morbidity exist.

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The authors have no conflicts of interest to declare.

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