"ELECTRONIC CALCULATOR OF CHRONIC PRURITUS": THE FIRST QUESTIONNAIRE FOR CHRONIC PRURITUS EVALUATION IN THE UKRAINIAN LANGUAGE

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Abstract

The first questionnaire for the assessment of chronic pruritus in the Ukrainian language has been developed on the basis of existing international validated questionnaires for itch and pain evaluation. The questionnaire developed has formed the basis for the computer program called "Electronic calculator of chronic pruritus". This application is designed for symptoms severity, patients' quality of life and treatment efficacy evaluation.

Key words: chronic itch, chronic pruritus, pruritus evaluation, questionnaire for the assessment of pruritus

Introduction. Pruritus (also known as itch) is a subjective, unpleasant sensation that causes an unbearable desire to scratch the skin and can have a significant adverse effect on the patient's quality of life (QL) [1, 2].

Pr may occur in isolation, accompany skin diseases, or be a major symptom of extracutaneous diseases (cancer, metabolic disorders, drug-related reactions, or infectious diseases) [1].

Depending on the duration of persistence, skin Pr is divided into acute and chronic.

Acute Pr is an extremely common sensation that almost every person, to one degree or another, has experienced, for example, after a mosquito bite or contact with a nettle [3].

According to the International Forum on the Study of Itch, chronic is called Pr lasting for 6 weeks or longer.

Recent studies have shown that the prevalence of chronic itch (CI) in the adult population reaches about 13.5%, as well as a tendency for its increase among the population compared with previous studies [4-6].

Depending on the localization, CI may be generalized or affect a separate area of the skin - localized Pr. The symptom is more common in women, and its incidence increases with age [5].

CI is a major symptom in many dermatological and systemic diseases. Like chronic pain, CI can adversely affect a patient's QL [3].

Recent studies have shown that CI can be as debilitating as chronic pain [7].

Pr intensity ranges from mild to severe and can have a significant psychosocial impact on the patient's daily activities and sleep [1].

There are many medicines available to ease itch, but none of them guarantees the complete elimination of this unpleasant sensations. Thus, it is extremely difficult to take this symptom, and especially its chronic form, under complete control [2].

Qualitative characteristics, intensity and daily rhythms of C are important factors that are of limited diagnostic importance today [6].

In our opinion, in order to further study the problem of CI, and to find alternative effective methods of its curation, domestic scientists need to be able to adequately assess the strength of manifestations and the effect of the symptom on the patient's QL, as well as to study the effectiveness of the prescribed treatment [8, 9].

The first step in the assessment of CI is to collect a detailed medical history and make accurate physical examination. Skin should be examined carefully for the identification of primary morphological elements [5].

Subsequent assessment of CI may be objective and subjective.

For the objective evaluation of itch they use accelerometers, actography, polysomnography and video registration of infrared radiation, which allow one to evaluate the behavior of scratching, not itch itself, as a symptom [10, 11].

In contrast to objective methods, existing gadgets measure various itch characteristics. In this regard, such estimation methods are considered more valid.

Subjective gadgets for itch evaluation are divided into one-dimensional and multidimensional.

One-dimensional gadgets, such as visual analogue scale, focus solely on itch's one aspect , thus giving only a partial evaluation of the symptom.

Multidimensional gadgets such as the Eppendorf Itch Questionnaire, the 5-D Itch Scale, the Itch Severity Scale and the Leuven Itch Scale consider itch in many aspects [2].

The objective: to develop a questionnaire for the evaluation of CI in the Ukrainian language and a technique for conversion the symptom into a numerical equivalent.

Materials and methods. Based on the existing validated questionnaires ("Eppendorf Itch Questionnaire", "Questionnaire for Pruritus Assessment", "McGill Pain Questionnaire", "Itch Severity Scale", "The 5-D Itch Questionnaire", "The Leuven Itch Scale", "The severity of Itch Profile Index"), as well as using the elements of the simplest gadget for the assessment of CI - "A Visual Analogue Scale ", we developed the first questionnaire for CI evaluation in the Ukrainian language. The latter formed the basis of the computer program" Electronic Calculator of Chronic Itch "[2 -19].

This program allows a physician to evaluate and compare the severity of the patient's CI and QL over the last month before, during and after treatment in numerical terms, based on the electronic survey questionnaire.

This article describes the technique and algorithm for estimating CI severity, specifically designed for the aforementioned device.

To elaborate a comprehensive itch integral evaluation, we used the answers to 24 questions from the developed questionnaire (Table 1). The survey involved 78 patients called on help in connection with CI (mainly from the Lviv region). In some cases, patients did not respond to certain survey questions. The share of missing answers was small and amounted to 0.75%. The calculations were performed in the R 3.2.3 statistical analysis environment using additional software packages to perform pcaMethods principal component analysis, FactoMineR factor analysis, and ggplot 2 imaging [20-22].

Table 1

The questions and the corresponding scales used to evaluate itch

ID	Question	Answer scale
1	2	3
V2	How often have you been itching in the last month?	0 - Never 1 - Rarely (one to several times a month) 2 - Sometimes (one to several times a week) 3 - Often (one to several times a day) 4 - Constantly

1	2	3
V3	What has been the average duration of one episode of itching in the last month?	0 -no 1 - 0 - 30 min 2 - from 30 - 60 min 3 - from 1 - 2 hours 4 - more than 2 hours
V5	Itching after mosquito bite	0 - 100*
V6	Itching intensity at the time of poll	0 - 100*
V7	The strongest manifestation of itching you have experienced in the last month	0 - 100*
V8	The weakest itching sensation you've had in the last month	0 – 100*
V9	Itching intensity over the last month (average)	0 – 100*
V10	Itch Exhaustion How exhausting has it been in the last month?	0 – 100*
Consequences of Itch for the last month		
V11	Appearance of scratching	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 - Constantly
V12	Exercise Restriction Through Itching	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 - Constantly
V13	Breaking my habitual routine	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 - Constantly
V14	Loss of appetite	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 - Constantly
V15	Violation of Social Contact Through Itching	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 - Constantly
V16	Changing Behaviors About Itching Through Itching	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 - Constantly

1	2	3
V17	Bad mood because of itching	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 - Constantly
V18	Reducing attention	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 – Constantly
V19	Disability	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 - Constantly
V20	Decreasing productivity at work / training	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 – Constantly
V21	Sleep Disorders Due to Itching	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 – Constantly
V22	Itching Awakening	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 – Constantly
V23	Accepting sleeping pills due to itching	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 – Constantly
V24	Reducing Sexual Attraction	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 – Constantly
V25	Reduced sexual activity	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 – Constantly

1	2	3
V26	Avoiding Intimate Life Through Itching	0 - Never 1 - Rarely 2 - From time to time 3 - Often 4 – Constantly

Note: * When calculating the integral C score using the arithmetic mean, the scale was reduced to 4 points by dividing by 25.

Questionnaire survey, clinical, analytical, comparative, statistical, computer technology were used in this research.

Results and discussion. The traditional way to form an integrated estimation on the base of questionnaires is score that is assigned to each answer. However, in the absence of separate answers, this approach leads to low values of the integral estimation. To get rid of the problem of missing individual answers we can by substituting the sum by the arithmetic mean. According to the law of large numbers, the empirical mean (arithmetic mean) of a sufficiently large finite sample from a fixed distribution is close to the theoretical mean (mathematical expectation) of this distribution. That is, the joint action of a large number of identical and independent random factors leads to a result that is practically independent of chance. In interpreting the law of large numbers, each questionnaire is an independent estimate of CI, which, however, is highly dependent on random factors and therefore has an unacceptable margin of error. By combining a large number of such estimates into a single integral estimate using the arithmetic mean, we obtain a measure that is virtually independent of chance and non-detectable error. On the other hand, considerable accuracy can only be achieved at the cost of a large volume of the questionnaire, so in practice there is always a trade-off between the accuracy of the questionnaire and its volume. Despite the undeniable advantages of a simple arithmetic method, there are several significant disadvantages associated with not complying with the statistical homogeneity of the questions:

1) some questions may systematically receive more or less points (center heterogeneity);

2) some questions may be more error-prone than others (heterogeneity of scale);

3) the answers to some questions may depend not only on the underlying factor (CI) but also on other, third-party factors (multifactorialism may lead to systematic inconsistency between the answers to some questions).

All of the disadvantages listed impair the accuracy of the trial results. However, there are methods for statistically treating these problems, including Principal Component Analysis (PCA) and Multiple Factor Analysis (MFA).

The PCA method finds such linear combinations of answers to the questions (principal components, PC) that the variance of patient projections on them will be maximized. In particular, assuming that different CI levels are the most important cause of variability in respondent responses, the first major component of PC1 will reflect the contribution of each question to the integral CI score, and the patients' projections on PC1 will correspond to the values of the integral CI.

At that, influence (the contribution to the integral assessment) of those answers that agree with one another are amplified, and those that contradict the main trend are weakened. The second major component of PC2 will reflect some other, third-party, factor-independent on CI influence but may influence a patient's choice.

Due to incomplete data (0.75%), the non-linear Iterative Projection on Latent Structures (NIPALS) algorithm was used instead of the traditional singular matrix decomposition. Before conducting the PCA, all survey results were centered and reduced to a single variance.

In analyzing PCA results, the structure and power of the most important major components are examined first and foremost. PC1 covers 36.4% of all variability in responses, which is more than 4 times the importance of the next PC2 component (covers 8.6% of variability).

The graph of the importance of the principal components on their ordinal numbers (Fig. 1) shows that the third and all subsequent principal components cover mainly the variability of random errors, since their importance is similar and decreases slowly. The significant importance of the first major component, in comparison to all others, is a sign of the successful design of the experimenter, most of which are consistent with each other, which in turn will ensure good reliability of the CI score obtained from it.
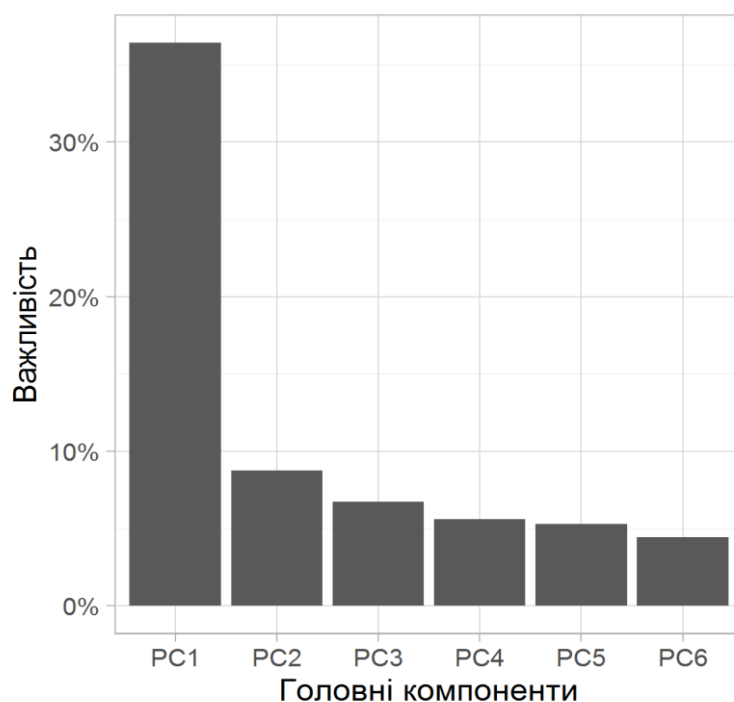
Fig. 1. The importance (variability covered) of the first six major components in PCA

The projection of the questionnaire on the first 2 main components allows to analyze the medical content of the components and to rank the questions according to the degree of influence on these components (Fig. 2). The mathematical basis for the principal component analysis shows that the first (principal) component will reflect an integral estimate of CI. The absence of negative projections of questions on the vector of the first principal component confirms that all questions are directed to the disclosure of the principal factor - CI, that is, the answers to different questions of the questionnaire do not contradict each other. At the same time, the most indicative and independent questions for the integral CI estimator are the questions with the largest projections: V22 (awakening through itch), V21 (sleep disturbance through itch) and V10 (exhaustion itch). Focusing most questions on the right side of Fig. 2 indicates that almost all the questions are sufficiently important for CI integral estimate. Virtually no effect on the integral estimate of CI revealed the question V5, which is not a surprise to us, because the essence of the issue was the evaluation of itch after the mosquito bite. On the contrary, these results confirm, in our opinion, the objectivity of the principal components analysis.
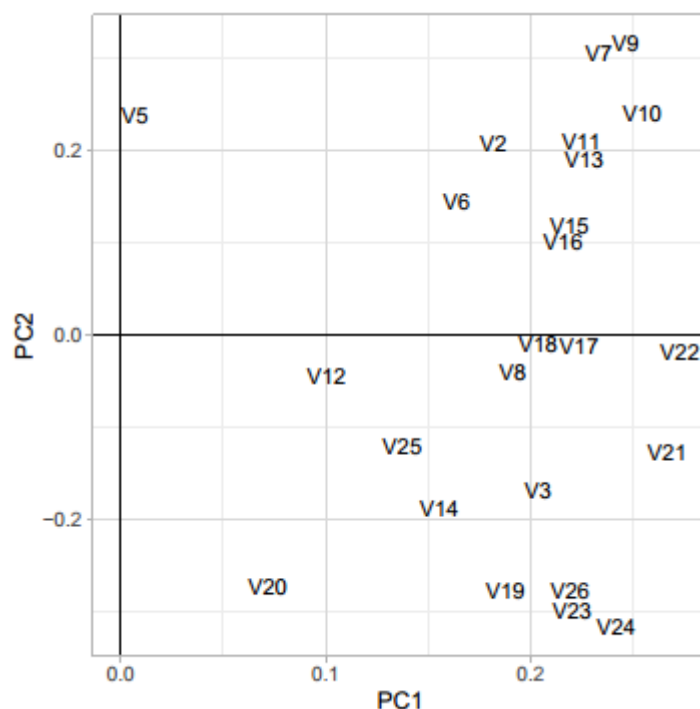
Fig. 2. Questionnaire projection on the first two main components

In addition, a weak role in itch estimation was demonstrated by questions V20 (decrease in productivity at work / study) and V12 (restriction of physical activity through itch). This can be explained by the fact that the answers to these questions depend more on the specifics of work and physical activity with which the respondent deals, than on itch intensity. It is interesting, in our opinion, to determine the medical nature of the second major component, because it is independent of the strength of CI factor that is unintentional, however, is also evaluated by the questionnaire developed. The biggest positive effects on the value of this factor are the high levels of answers to questions V9 (itch intensity in the last month), V7 (the strongest manifestation of itch that you have experienced in the last month), V10 (fatigue of CI; how exhausting was it in the last month?) and V5 (itch after mosquito bite). Based on the nature of these questions, the second major component can be identified as individual sensitivity to itch, which in turn may include both the individual level of nervous system irritability in response to biochemical processes underlying the itch phenomenon and the subjective emotional response to it. In particular, the high score of a patient with his / her itch may be due to both a truly severe disease course and high individual sensitivity with a moderate or even weak clinical course of the disease. Thus, our calculations indicate the need to decompose the subjective assessment of a patient's itch into an objective component that is independent of individual perception and should correlate with the intensity of the

biochemical processes underlying pruritus, and a subjective individual component that depends solely from the constitution of the nervous and mental systems (temperament and character). The very objective component, which in our study is represented by the integral itch estimator (the first principal component), should be considered as a clinical indicator for the evaluation of the patients' condition and the studies of the efficacy of treatment against CI.

And only on the basis on integral estimation of itch, free from patient's personal perception and personality traits, certain medical decisions should be made. At the same time, according to the coordinates of the questions on the plane of the first 2 main components (Fig. 2), the patients' assessment of CI intensity (V9), its strongest manifestation (V7) and exhaustion (V10) in the last month contains in almost equal parts and objective , and subjective components. Also, in our opinion, the questions at the bottom of Fig.2 are of interest for the analysis of subjective perception of itch. These questions have negative projection values for PC2 and high enough projection values for PC1, and therefore positive answers are indicative of an objectively severe pathological pruritus with relatively low psychological response to overall itch, such as from a mosquito bite. Such questions include V24 (reduction of sexual desire), V23 (reception of sleeping pills through itch), V26 (avoidance of intimate life through itch), V19 (disability). Patients who answer yes to these questions have such severe difficulty because of itch that they assess its level from mosquito bite at a very low one, making their problem more pronounced by contrast.

As a result of our analysis of the principal components for each patient, his or her PC1 coordinate, which is an integral estimate of pruritus, was calculated and, as we showed above, is intended to reflect the objective side of the biochemical processes at its base, as well as a PC2 coordinate that reflects the level of psychological level sensitivity to itch. Visualization of these coordinates (Fig. 3.) indicates that the integral estimate of itch is still related to the individual perception of this symptom by nonlinear dependence. In particular, although the overall correlation between PC1 and PC2 is virtually indistinguishable from 0 (this is a direct consequence of the orthogonality of the principal components in PCA), in the interval for PC1 values <1 the correlation between PC1 and PC2 is positive (r = 0.48, p = 0.00032), and in the interval for PC1 values> 1 the correlation between PC1 and PC2 becomes negative, also with statistical significance (r = 0.40, p = 0.045). This means that the relationship between integral score of itch and individual sensitivity to it is different depending on the severity of itch. In weak itch, patients who respond sensitively to the one from a mosquito bite, at the same time, have a higher itch score than their existing illness. Conversely, those who are not responding to the mosquito bite have low itch strength due to the disease. That is why there is a positive

correlation between the 2 main components in the left part of Fig. 3. In this case, the person's assessment of ones own sensitivity to itch (PC2) is more objective and influences the assessment of itch strength (PC1). In other words, most patients in the PC1 <1 segment should not be differentiated by itch intensity, but should be considered as having poor pruritus of approximately the same intensity. However, at high itch intensity due to illness, the relationship between PC1 and PC2 becomes reversed. The patient evaluates his / her pruritus in relation to a certain internal standard, and the questionnaire design suggests that the reference be used as a reference after the mosquito bite. Thus, to emphasize the strength of itch from the disease, the patient slightly lowers his or her itch score after mosquito bites, so as to reflect the contrast between the two conditions. That is, the assessment of patients own itch (PC1) is now more objective and influences the assessment of individual sensitivity to it (PC2). This leads to a negative correlation between PC1 and PC2 in patients with severe pruritus.
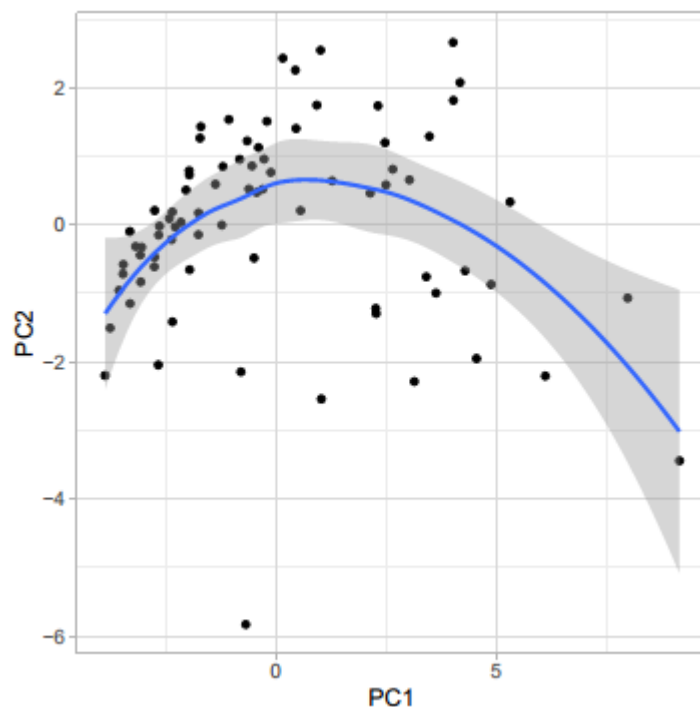

Fig. 3. Projections of patients on the plane of the first 2 main components

Due to the peculiarities of the PCA method, each of the principal components is constructed in such a way that the arithmetic mean of the patients' projections to the principal component is practically equal to 0. Such a scale is not user-friendly, and so we have delivered to a format when absolute minimum pruritus according to the questionnaire was equal to 0 points. Thus, all the scores on the given scale will be 6.53 points higher than the

PC1 values shown in the figures. The weights that must be applied to each of the answers in order of their addition to get the value of integrated estimation of itch we have developed are given in Table. 2 (ranked by descending weight of questions).

Table 2

Scales for the calculation of the integral itching score

ID	Questions	coefficient
V8	The weakest itching feeling you've had in the last month	0.76
V24	Reducing Sexual Attraction	0.55
V19	Disability	0.54
V25	Reduction in sexual activity	0.48
V9*	Last month's itching intensity (average)	0.43
V3	What has been the average duration of one episode of itching in the last month?	0.42
V14	Loss of appetite	0.38
V2	How often have you been itching in the last month?	0.36
V23	Acceptance of sleeping pills through Itching	0.35
V22	Itching Awakening	0.33
V7*	The strongest manifestation of itching you have experienced in the last month	0.32
V6*	Itching intensity at the time of the poll	0.31
V15	Violation of social contacts through itching	0.31
V26	Avoiding Intimate Life Through Itching	0.31
V13	Violation of my usual household activities	0.25
V16	Changes in the behavior of others through itching	0.25
V10*	Itching exhaustion. How exhausting has it been in the last month?	0.24
V18	Reduced attention	0.24
V11	The appearance of a feud	0.22
V21	Sleep disturbance due to pruritus	0.21
V17	Bad mood because of itching	0.20
V20	Reduced productivity / training	0.17
V12	Exercise Restriction through Itching	0.17
V5*	Itching after mosquito bite	0.01

Notes: * Answers to these questions should be converted from a 100-point to a 4-point scale by dividing by 25 before applying the ratio.

Multiple factor analysis (MFA) is basically similar to principal component analysis. The difference between these 2 approaches is that the PCA aims to maximize the entire variability of the result matrix, while the MFA tries to find only a small number of latent factors, rejecting excess variability as a measurement error or as individual variability of a trait that is not related to the total variability. MFA is more costly in calculations, however, it is possible to correctly distinguish the factor structure of the studied result matrix in difficult

cases where PCA is not able to perform the correct factorization. The use of MFA for analyzing the results of a patient survey with the aim to develop an integral pruritus score gives almost identical with PCA results for different variants of feature grouping. The structure of the first 2 factors replicates the structure of the first 2 major components, and the calculated itch levels strongly correlate with the value of $r = 0.991$ (Fig. 4). Therefore, the results of the principal component analysis are taken as the basis and the MFA model has not been analyzed further.
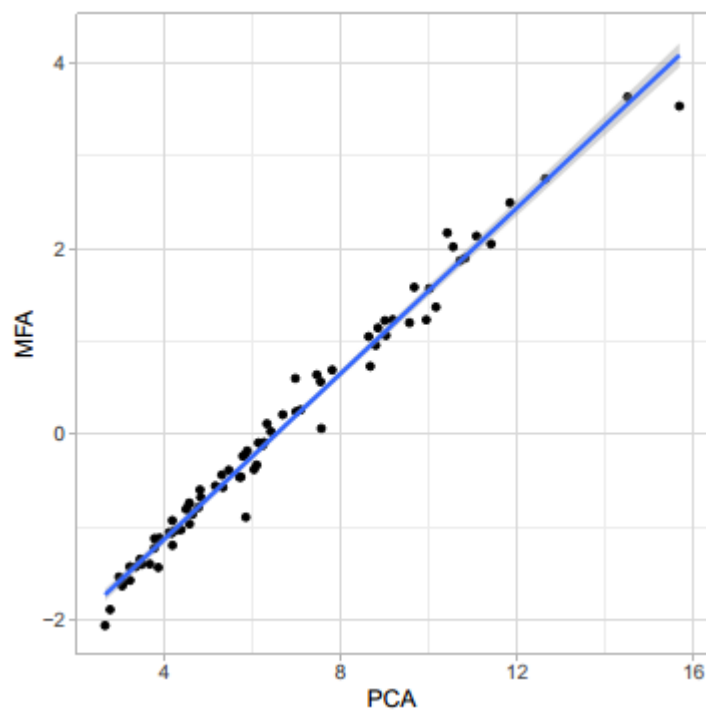

Fig. 4. Correlation between itching estimates by multiple factor analysis and principal component analysis

Conclusions

1. The benefits of the new questionnaire are comprehensive approach to the symptom of CI, taking into account most important aspects, including the possibility of the questionnaire using for patients with CI of different etiology and the possibility of its re-use to evaluate the effectiveness of the prescribed therapy.

2. By integrating the main components of patient questionnaires on various aspects related to CI, its integrated assessment is developed and mathematically substantiated. The structure of the matrix of survey results indicates that the problem of pruritus should be

decomposed into 2 components: the objective component, which is determined by the integral assessment, as well as the subjective component, which depends on the individual psychological sensitivity and perception of CI.

3. In general, almost all the answers to the questionnaire showed significant contributions to the integrated evaluation of CI, which, in our opinion, testifies to the questionnaire's successful design.

4. The best correlation with the integrated assessment of itch is demonstrated by the answers to the questions about the facts of awakening through it, disturbance of falling asleep through this symptom and the exhaustion it. In addition, a complex nonlinear relationship between the assessment of individual pruritus sensitivity and the evaluation of its intensity is noted and substantiated.

5. Further studies of the correlations of the integral evaluation of itch with the levels of biochemical markers of inflammation and excessive immune response are needed to experimentally confirm the objective nature of our scale offered. In case of successful validation of the scale described, it can be used as a basis for making medical decisions, as well as for evaluating the success of therapy of dermatological diseases.

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