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Clinical utility of biomarkers of the hand in the diagnosis of schizophrenia

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ABSTRACT

A number of biomarkers were assessed in photos and prints of the hands of 95 patients with a variety of mental disorders to determine whether patients with schizophrenia could be distinguished from the others. Patients were recruited as consecutive admissions from an outpatient psychiatric day hospital population. Fourteen patients were diagnosed with schizophrenia/schizoaffective disorder and 81 were diagnosed with other mental disorders. A discriminant analysis yielded an overall 80% correct classification, with a sensitivity (schizophrenia patients identified correctly) of 78.6% and a specificity (non-schizophrenia patients identified correctly) of 80.2%. Significant differences were noted in the proximal interphalangeal joint, eponychium of the middle digit and fingernails. To determine biomarker frequency distribution patients with bipolar disorder were then compared to those with schizophrenia/schizoaffective disorder and then to patients with PTSD. The former yielded an overall 78.6% correct classification, with a sensitivity of 71.4% and a specificity of 85.7% and with similar biomarker frequency distribution for bipolar disorder as for the entire non schizophrenia group. The latter comparison yielded an overall 58.6% correct classification, with no significant differences between the features. The application of these biomarkers in clinical practice could constitute an additional tool for the psychiatrist in cases lacking diagnostic clarity.

1. Introduction

In the absence of an objective test, the diagnosis of schizophrenia depends upon a collection of clinical features including symptoms, their associated chronological and functional characteristics and exclusion criteria (American Psychiatric Association, 2013; World Health Organization, 1992). Sources of information including the subject's account, clinical records, and observations of family members may be impacted by the unwillingness or inability of many patients to communicate their symptoms and the subjective assessments of clinical evaluators resulting in significant shifts in diagnosis over time. In one study (Heslin et al., 2015) over the course of a decade about one third of participants originally given a non-schizophrenia diagnosis had gradually shifted to a diagnosis of schizophrenia while others remained a diagnostic uncertainty. Since longer periods of untreated psychosis are associated with poorer prognoses (Penttilä et al., 2014), an accurate test would enable early intervention and improve patient outcomes, providing significant reductions in patient morbidity and health care costs. Consequently, one or more biomarkers capable of distinguishing patients with schizophrenia from healthy controls and from those with other mental disorders has been sought. While several hematologic or genetic biomarkers have been suggested (Lawrie et al., 2011) a non-invasive test for schizophrenia now being considered is based on minor physical abnormalities.

Minor Physical Anomalies (MPAs) refer to subtle morphological deviations that are of little functional or cosmetic consequence but may represent markers for underlying disease or disease susceptibility (Compton and Walker, 2009). These include, among others, aberrations in the distal upper limb, especially abnormalities in the palmar creases, and the shape of the fingers and fingernails (Gourion et al., 2004; Xu et al., 2011). Dermatoglyphic configurations in the palm are also a possible marker for associated genetic aberrations, and some clinical syndromes (Pratibha et al., 2011). From an embryological perspective the distal upper limb is closely related to brain development both

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Table 1
List of six hand biomarkers that were examined.

Biomarker	Location	Information source	Scale
Proximal interphalangeal joint (PIP)	Middle digit	Photograph	1 = Poorly defined skeletal borders to 0 = Intermediate or well defined skeletal borders
Eponychium of the middle digit	Distal phalanx of middle digit (nail)	Photograph	1 = Growth extending over the lunula and beyond 0 = Normal
Fingernails	fingernails	Photograph	1 = small size fingernails 0 = normal
Proximal transverse crease (PTC)	Proximal palmar flexion crease	Photograph and print	1 = shortened and/or fragmented in at least one hand 0 = normal
Thenar crease (TC)	Thenar Crease	Photograph and print	1 = ill defined in at least one hand 0 = normally distinct
Digital flexibility	Digits	Manual examination	1 = rigid to 4 = very flexible (about 90°)

sharing ectodermal origins and developing at the beginning of the second trimester with possible functional growth dependencies later (Bracha et al., 1991). Differences in the prevalence of aberrations of the distal upper limb have been reported in individuals with schizophrenia compared with controls (Fatjó-Vilas et al., 2008; Weinberg et al., 2007). Although numerous studies have reinforced the correlation between MPAs of the distal upper limb and schizophrenia they have not yet been considered of diagnostic utility in clinical work.

In 2013 and again in 2015, we described a model for identifying patients with schizophrenia according to a combination of aberrant features of the distal upper limb based on previously suggested criteria (Holtzman, 1983, 2004) The initial model was composed of three biomarkers including dermatoglyphic and digital features which were able to distinguish patients with schizophrenia from controls with an overall accuracy of 81.2% (Shamir et al., 2013). Subsequently the model was widened to five biomarkers which were able, in a male population, to distinguish schizophrenia patients from a disparate group of other mental disorders as well as controls with an overall accuracy of 78.4% (Shamir et al., 2015). By validating the original biomarkers and displaying a notable lack of difference between patients with other mental disorders and the control group, these results suggested albeit inconclusively that the chosen biomarkers could be confined to schizophrenia.

The first purpose of the present study is to test the applicability of the previously identified biomarkers of the hand associated with schizophrenia to a group of patients admitted over a year and a half to an ambulatory psychiatric day hospital. In addition, it was thought that an expanded group of patients with non-schizophrenia mental disorders might assist in clarifying whether the biomarkers identified are limited to schizophrenia. We aimed also to evaluate the potential utility of the biomarkers of the hand as an auxiliary diagnostic tool in a clinical setting.

2. Methods

2.1. Subjects

103 consecutive patients with diverse psychiatric disorders admitted for treatment to the psychiatric day hospital were recruited for the study by the attending psychiatrist at the Tel Aviv Sourasky medical Center in central Israel between January 2015 and July 2016. All participants gave written informed consent after receiving a full explanation regarding the study protocol. All participants were fluent in Hebrew with satisfactory language comprehension. The study was approved by the Institutional Review Board of Tel Aviv Sourasky Medical Center and patients were examined in accordance with the hospital's Helsinki committee.

All subjects underwent a complete medical evaluation as part of their admission to the psychiatric facility and medical records were reviewed following completion of the study. Exclusion criteria included psychiatric disorders following head injuries and those with associated non psychiatric anatomical or functional neurological disorders such as agenesis of the corpus callosum, epilepsy or Parkinson's disease. Eight subjects were excluded on this basis, with 95 participants remaining in the study. Confounding variables with regard to hand evaluations such as associated arthritic conditions and developmental abnormalities were also considered a criterion for exclusion but none of the subjects were thereby excluded.

2.2. Tools

Data collection included a set of 12 hand photographs for each subject, in several given positions including dorsal and volar aspects of the hand. The photos were taken with a hand held digital camera and were all taken in accord with printed instructions and illustrations. Criteria, as in previous studies (Shamir et al., 2015), included camera angle, white background, avoidance of shadows, and general composition to minimize possible inaccuracies and biases in evaluation of the

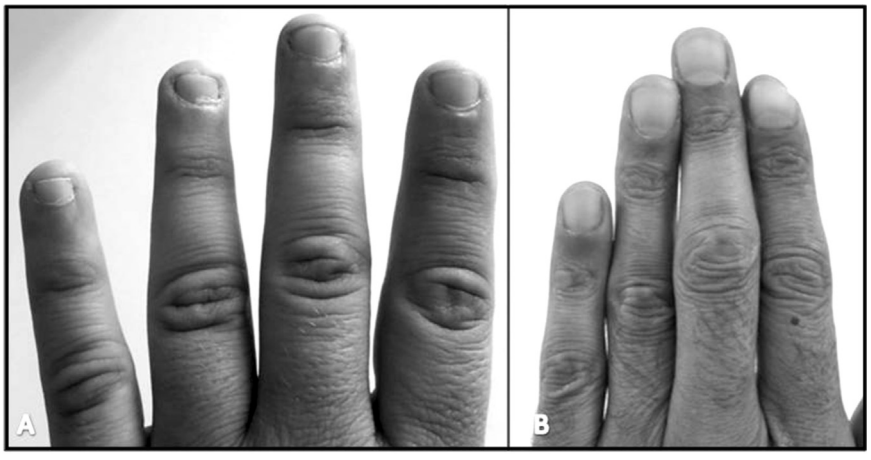

Fig. 1. (A) Small nails on the hands of an adult suggestive of schizophrenia (B) Normal sized nails.

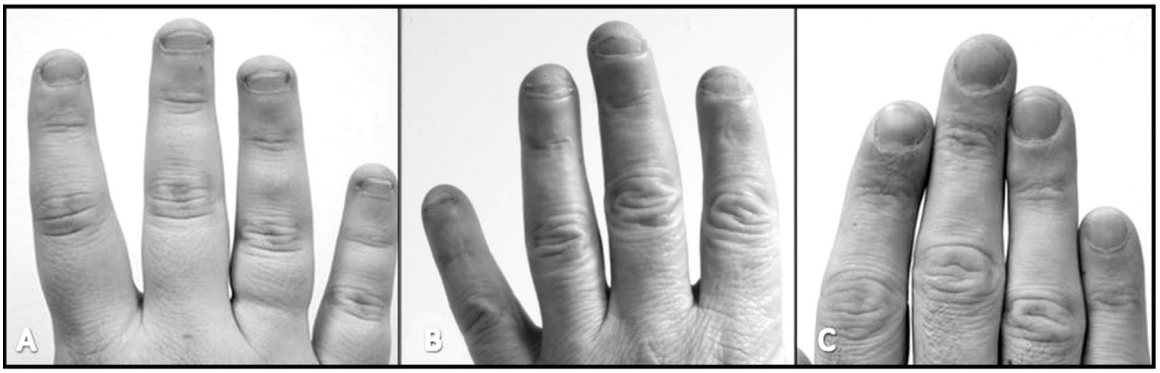

Fig. 2. (A, B) The extension of the eponychium well over the base of the nail along with the poorly defined proximal interphalangeal joints are biomarkers which may contribute to a diagnosis of schizophrenia (C) Normal eponychium and joint definition.

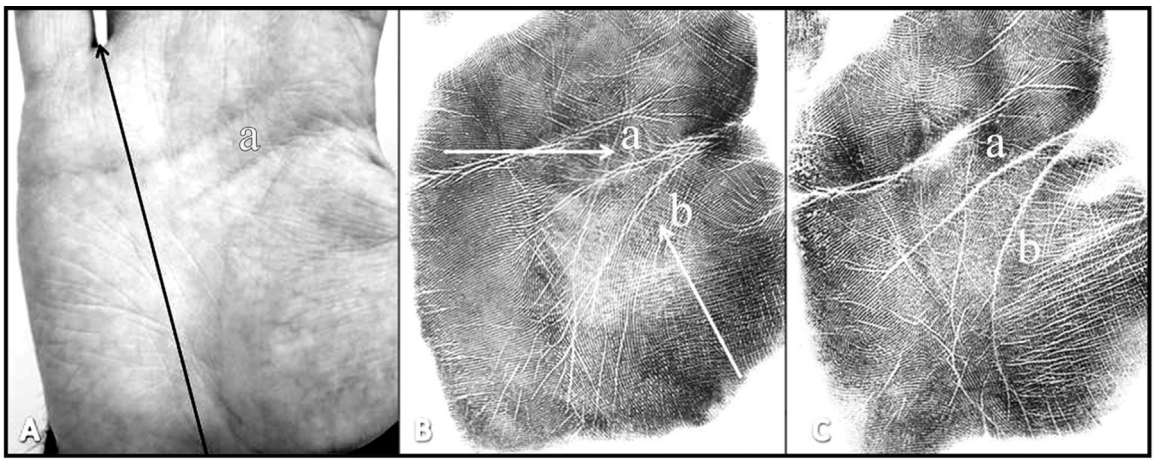

Fig. 3. Dermatoglyphic anomalies: A (a) short Proximal Transverse Crease B. (a) Severe fragmentation of the Proximal Transverse Crease (b) fragmented Thenar Crease. These have previously been associated with schizophrenia. (C) (a) Proximal Transverse Crease, and (b) Thenar Crease, both without anomalies.

palms and digits. Handprints of both hands, palms and fingers were done on white paper using a black water-based ink. Six hand biomarkers were examined (see Table 1), five comprising the model used in the previous study including (1) an ill defined proximal interphalangeal joint (PIP) (Fig. 2) (2) an extended eponychium (proximal nail fold) of the middle digit (Fig. 2) (3) an ill defined thenar crease (TC) (Fig. 3) (4) an abnormality in the proximal transverse crease (PTC) described either as a shortened crease terminating in the middle of the palm and not extending beyond the midline of the ring digit, and/or a broken or fragmented crease (Fig. 3) and (5) the degree of "flexibility" of the fingers. An additional biomarker was added - small fingernails described as fingernails notably diminished in size and distinct from the influence of eponychial overgrowth (Fig. 1) (Gourion et al., 2004). Unlike normal nails in which the distal edge of the nail extends almost the entire width of the distal phalanx small fingernails are notably narrower at the distal end and extend proximally in a V shape for a length roughly equal to its distal width.

2.3. Procedure

Five biomarkers (out of the six) of the hand were examined and rated by two judges who were both knowledgeable in the appraisal of features of the hand based on photos and prints and blind to the diagnoses of the patients. Working together they reached a mutual decision regarding the degree of severity and numerical rating of each of the five elements of the hand. The sixth biomarker, flexibility of fingers, was rated by one of the authors A.L. who collected the data and was also blind to the diagnoses of the patients. The results were then submitted for statistical evaluation.

2.4. Statistical analysis

In order to differentiate between schizophrenia patients and patients with other mental disorders, a discriminant analysis was performed entering all six predictors together. Due to the small number of schizophrenia patients in the sample, we aimed at calculating a more balanced discriminant analysis based on a similar number of schizophrenia patients and patients with other disorders. In order to avoid a single biased sample of patients with other mental disorders, ten different samples were randomly selected, and accordingly ten discriminant analyses performed using each of the samples of patients with other mental disorders together with all the schizophrenia patients. Furthermore, each discriminant analysis was performed using the leave-one-out cross-validation method (which is a variant of the k-fold cross validation, and recommended especially for small samples), entering all six predictors simultaneously. The outcomes of the analyses were averaged beyond samples. Two additional discriminant analyses were performed between schizophrenia and bipolar patients, and between PTSD and bipolar patients. In addition, in order to compare the distributions of each of the six predictors between schizophrenia and non-schizophrenia patients, and to compare gender distributions between the groups, chi square tests for independence were performed. In cases with more than 20% of cells with expected values smaller than 5, Fisher exact tests were used. Mann-Whitney *U*-test was used to compare ordinal variables between males and females.

3. Results

Of the 95 patients 14 carried a diagnosis of schizophrenia/

Table 2
Distribution of diagnoses among patients with mental disorders other than schizophrenia/ schizoaffective.

ICD 10 code	Diagnosis	N (%)
F31	Bipolar Affective disorder	14 (17.3)
F32-F34	Depressive disorders	29 (35.8)
F41	Anxiety disorders	3 (3.7)
F42	Obsessive Compulsive Disorder (OCD)	5 (6.2)
F43	Post Traumatic Stress Disorder (PTSD)	15(18.5)
F60	Personality Disorder	15 (18.5)

schizoaffective disorder (Schizophrenia patients = 11, schizoaffective patients = 3) and the remaining 81 patients were diagnosed with other mental disorders not in the schizophrenia spectrum. Table 2 shows the distribution of diagnoses among patients with mental disorders other than schizophrenia/schizoaffective disorder. Patients' diagnoses were assigned in accordance with ICD-10 criteria by the treating psychiatrist.

The schizophrenia group consisted of 9 males and 5females and the non schizophrenia group was comprised of 34 males and 47 females. A chi-square test of independence found no significant gender composition differences between the groups. $\chi^2(1, N = 95) = 2.40\ p = 0.12$.

Significant differences were obtained between males and females for flexibility (Mann-Whitney U test, $p = 0.013$; females (mean = 2.33, sd = 1.00) showed larger flexibility compared to males (mean = 1.79, sd = 0.86) and for the overgrowth of the eponychium on the middle finger (Fisher exact test, $p = 0.02$) found among 32.6% of males while only among 11.5% of females.

No significant differences were obtained in age distribution. Schizophrenia patients age ranged between 19 and 62 years (mean = 41.36, S.D. = 14.28) and among those with other mental disorders between 21 and 69 years (mean = 41.99, S.D. = 12.85; $t(93) = 0.17$, $p = 0.89$. Subjects in both groups were of Jewish heritage and of mixed Ashkenazi and Sephardic descent.

The discriminant analysis, aiming to discriminate between schizophrenia and patients with other mental disorders yielded a Wilks' lambda of 0.76 ($\chi^2(6) = 25.34$, $p < 0.001$; see Table 1). The standardized canonical discriminant coefficients for the six discriminant variables were PIP = 0.36, PTC = 0.11, eponychium of the middle digit = 0.60, small fingernails = 0.50, TC = −0.19, flexibility = 0.32. The functions at group centroids were −0.23 for patients with other mental disorders, and 1.36 for schizophrenia patients. This model yielded an overall 80% correct classifications, with a sensitivity (schizophrenia patients identified correctly) of 78.6% and a specificity (non-schizophrenia patients identified correctly) of 80.2% ($n = 95$, 14 schizophrenic patients and 81 patients with other mental disorders).

The outcomes of the ten discriminant analyses, based on ten different random samples of 14 patients with other mental disorders, combined with the 14 schizophrenia patients were averaged between samples. The average Wilks' lambda reached a value of 0.58 (Average $\chi 2(6) = 12.64$, p = 0.06). The averaged standardized canonical discriminant coefficients were PIP = 0.30, PTC = 0.11, eponychium of the middle digit = 0.71, small fingernails = 0.47, TC = −0.24, flexibility = 0.01. The functions at average group centroids were −0.82 for patients with other mental disorders, and 0.82 for schizophrenia patients. These models yielded an average overall 77.5% correct classifications, with a sensitivity of 70.7% and a specificity of 84.3%. The leave-one-out validation yielded an average of 67.2% correct classification with an average sensitivity of 60.7% and specificity of 73.6%.

Table 3 presents the distribution of the discriminating variables, separately for patients diagnosed with schizophrenia and for patients with other mental disorders. As can be seen in the table, schizophrenia patients differed significantly in eponychium of the middle digit, nail development and proximal interphalangeal joint. Table 4 presents the distribution of the discriminating variables among the other mental disorders including Bipolar disorder, Depressive Disorder, OCD, PTSD and Personality disorder.

Following the initial results and in order to examine why some biometric parameters in this study were not significant compared with prior studies two additional comparisons were performed, one comparing patients with schizophrenia/schizoaffective disorder and patients with bipolar disorder and another comparing patients with Post Traumatic Stress Disorder (PTSD) and patients with bipolar disorder. In the first analysis (schizophrenia/schizoaffective patients vs. bipolar patients) Wilks' lambda reached a value of 0.61 ($\chi^2(6) = 11.5$, $p = 0.07$). The standardized canonical discriminant coefficients were: PIP = 0.53, PTC = −0.22, eponychium of the middle digit = 0.54, small fingernails = 0.35, TC = −0.03, flexibility = 0.42. The functions at group centroids were −0.78 for patients with a bipolar mental disorder, and 0.78 for patients with schizophrenia.

This model yielded an overall 78.6% correct classifications, with a sensitivity of 71.4% and a specificity of 85.7% ($n = 28$, 14

Table 3
Distribution of the discriminating variables separately for patients diagnosed with schizophrenia and for those with other mental disorders and Fisher's Exact/ Mann-Whitney U Test comparing the distributions of the two groups.

Variable		Schizophrenia patients (%)	Patients with other mental disorders (%)	*df*	*p*
Proximal interphalangeal joint (PIP)				1	0.02*
	Well defined and/or Intermediate	42	77.8		
	Poorly defined	58	22.2		
Proximal transverse crease (PTC)				1	1
	Normal	50	51.9		
	Shortened and/or fragmented	50	48.1		
Eponychium of the middle digit				1	0.0001**
	Normal	42.9	85.2		
	Growth extending over the lunula and beyond	57.1	14.8		
Small fingernails				1	0.001**
	Normal	42.9	85.2		
	Small in size	57.1	14.8		
Thenar Crease				1	0.92
	Normal	50	48.1		
	Ill defined	50	51.9		
Digital flexibility					0.43
	Rigid	28.6	34.6		
	Semi rigid	28.6	34.6		
	Semi flexible	28.6	22.2		
	Flexible	14.2	8.6		

* $p < 0.05$.
** $p < = 0.001$.

Table 4
Distribution of the biomarkers for patients diagnosed with other mental disorders.

Variable		Patients with bipolar disorder (%)	Patients with Depressive disorders (%)	Patients with OCD disorders (%)	Patients with PTSD (%)	Patients with Personality disorder (%)
Proximal interphalangeal joint (PIP)	Well defined and/or Intermediate	85.7	72.4	100	73.3	80
	Poorly defined	14.3	27.6	0	26.7	20
Proximal transverse crease (PTC)	Normal	50	51.7	40	40	66.7
	Shortened and/or fragmented	50	48.3	60	60	33.3
Eponychium of the middle digit	Normal	85.7	82.8	80	93.3	80
	Growth extending over the lunula and beyond	14.3	17.2	20	6.7	20
Small fingernails	Normal	85.7	89.7	60	86.7	86.7
	Small in size	14.3	10.3	40	13.3	13.3
Thenar Crease	Normal	50	48.3	60	53.3	46.7
	Ill defined	50	51.7	40	46.7	53.3
Digital flexibility	Rigid	42.9	37.9	20	26.7	26.7
	semi rigid	28.6	24.1	80	40	40
	semi flexible	28.6	24.1	0	26.7	20
	Flexible	0	13.8	0	6.7	13.3

schizophrenia patients and 14 bipolar patients). A Fisher's Exact Test comparing the distributions of the two groups yielded a significant difference for the PIP, eponychium of the middle digit and fingernails. The PTC showed a non significant prevalence for more severe anomalies in the schizophrenia group compared with the bipolar group.

In the second comparison (Bipolar patients vs. PTSD patients) Wilks' lambda reached a value of 0.92 ($\chi^2(6) = 2.04$, $p = 0.92$). The standardized canonical discriminant coefficients were: PIP = −0.56, PTC = 0.52, eponychium of the middle digit = −0.57, small fingernails = 0.07, TC = −0.58, flexibility = 0.41. The functions at group centroids were 0.30 for patients with bipolar mental disorder, and 0.28 for patients with PTSD. This model yielded an overall 58.6% correct classification, with 57.1% of bipolar patients identified correctly and 60% PTSD patients identified correctly ($n = 29$, 14 Bipolar patients and 15 PTSD patients). A Fisher's Exact Test comparing the distributions of the two groups yielded no significant differences in the hand features between the groups.

4. Discussion

The results demonstrate that a combination of biomarkers of the hand were able to distinguish patients with schizophrenia from those with other mental disorders as 78.6% of schizophrenia patients and 80.2% of non-schizophrenia patients were identified correctly. Although this suggests that the biomarkers chosen in combination may be specific for schizophrenia more studies inclusive of larger numbers of individual psychiatric disorders would be needed. Singling out the small number of schizophrenic patients among a much larger group of non schizophrenia patients in the current study highlights the sensitivity of this particular combination of biomarkers. The sensitivity approximates that of the previous study (Shamir et al., 2015) in which schizophrenia constituted a larger proportion of the study patient population although some variation in the biomarkers was used in each study.

Patients with schizophrenia demonstrated significant anomalous eponychial overgrowth of the middle digit, small fingernails and poor definition of PIP skeletal borders. Although anomalies in the PTC were not significantly different between the two groups, the degree of anomaly was more severe among schizophrenia patients. As in the prior study there was no significant difference in the TC, as defined, between the two groups with a 50% frequency of anomalies in both. Unlike the prior study, however, the degree of flexibility was not significantly different between the two groups.

A number of factors may have accounted for the differences in the significance of individual schizophrenia associated biomarkers previously identified (Shamir et al., 2015). The prior study was limited to males while the current study included 5 female schizophrenia patients, about 35% of a small group but one with its own possible individual variants. Some of these identified in the current study include differences in eponychial overgrowth and finger flexibility. The diagnoses of the non schizophrenia group and their relative numbers varied between the two studies some components of which may have impacted the results. The possibility that one or more of the biomarkers may not be confined to schizophrenia would be more evident in the current study since the prior non schizophrenia group was merged with a control group.

We examined the possibility that the differences in biomarker significance observed in this study compared to prior studies were due to differences in biomarker frequency distribution in patients with other mental disorders. In a statistical analysis limited to patients with bipolar disorder the biomarkers successfully distinguished those with schizophrenia from the bipolar patients and with similar biomarker frequency distribution for bipolar disorder as for the entire non schizophrenia group. It made no distinction between those with bipolar disorder and patients with PTSD, another non schizophrenia disorder. This demonstrates that these biomarkers can as readily distinguish schizophrenia from bipolar disorder as a single entity as they can from the entire non schizophrenia group. As PTSD would not be expected to demonstrate developmental aberrations of the hand the failure to distinguish bipolar disorder from PTSD suggests that either the patients with bipolar disorder lacked developmental aberrations of the hands or that, if present, these particular biomarkers were unable to recognize them. The prevalence of MPAs in bipolar disorder has been previously examined and compared to that in schizophrenia. Generally, bipolar patients exhibited a lower rate of MPAs than Schizophrenia patients (Green et al., 1994; Trixler et al., 2001) but an equal or higher rate than controls (Berecz et al., 2017). The ability to differentiate patients with bipolar disorder from those with schizophrenia spectrum disorders, with an overall 78.6% correct classification is particularly noteworthy. This differentiation is of outmost importance because there might be great resemblance in the symptoms of bipolar affective disorder, schizoaffective disorder, and schizophrenia i.e. psychotic symptoms, affective instability, negative symptoms, and to some extent cognitive impairment (Green, 2006). In addition, schizophrenia and bipolar disorder partly share a genetic predisposition. (Purcell et al., 2009) Therefore, the clinical necessity of distinguishing those two similar conditions is especially important.

Only two out of the six biomarkers utilized in the current study were

previously associated with schizophrenia - small fingernails (Gourion et al., 2004) and anomalies of the PTC (Bracha et al., 1991; Fatjó-Vilas et al., 2008) but they were evaluated individually and not as part of a combination of biomarkers which encompasses morphological and dermatoglyphic features of the distal upper limb. The association of small fingernails with schizophrenia was reaffirmed in the current study. These were present in 57.1% of schizophrenia patients and only 14.8% of those with other mental disorders. While eponychial extension over the nail in schizophrenic patients was also significant, unusual visibility of the eponychial vascular plexus in schizophrenia subjects has previously been documented (Curtis et al., 1999) and may be a related feature.

It is noteworthy that the study design did not include a control group of healthy individuals, since most of the biomarkers used had previously been evaluated using a control group of healthy individuals either by itself (Shamir et al., 2013) or in conjunction with a diverse group of non schizophrenic mental disorders including those represented here (Shamir et al., 2015). In each case they succeeded in identifying patients with schizophrenia.

The study has a number of limitations. Some of the patients with non schizophrenic mental disorders may have had more than one diagnosis thereby impacting the numbers in each category. Patients were assigned to the category reflecting their primary diagnosis.

Additionally regarding statistical analysis, it is important to mention that although overall prediction accuracy in the discriminant analysis was relatively high, the sensitivity obtained (78.6%) was not high enough, as statistic standards suggest values higher than 90%.

5. Conclusions

A number of biomarkers of the hand applied together were able to distinguish patients with schizophrenia/schizoaffective disorder from patients with a number of other unrelated mental disorders, and in particular from bipolar disorder. Several nail related anomalies including eponychial overgrowth and small fingernail size together with poor definition of the skeletal borders of the proximal interphalangeal joint constituted the main distinguishing biomarkers. The application of these biomarkers in clinical practice could constitute an additional tool for the psychiatrist in cases lacking diagnostic clarity.

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