Clin Schizophr Relat Psychoses
Volume 15s:1, 2021
DOI: 10.3371/CSRP. IMKA.021221

Clinical Schizophrenia & Related Psychoses

Research Article

Hybrid Open Access

Clinico-Epidemiological Comparison of Delusion Prominent and Hallucination Prominent Clinical Subgroups of Paranoid Schizophrenia Outpatients

Anatoly Kreinin[1*], Mariia Ivenski[1], Dmitry Ivenski[1] and Michael Kirby[2]

[1]*Maale Carmel Mental Health Center, Israel Institute of Technology, Haifa, Israel*

[2]*Department of Molecular Biology, Ariel University, Ariel, Israel*

Abstract

Objective: The primary goal of this replication study was to confirm previous findings which demonstrated that there are epidemiological and clinical differences between the hallucinatory and delusional subgroups of patients diagnosed with paranoid schizophrenia. In contrast, and as an extension to the previous study, which evaluated hostel patients, the in the current study we evaluated outpatients with paranoid schizophrenia. In addition, we sought to verify our assertion that within the spectrum of schizophrenia disorders, among patients with paranoid schizophrenia there are at least two sufficiently homogeneous subgroups with distinctive clinical and epidemiological characteristics.

Methods: Paranoid schizophrenia outpatients (n=100) meeting inclusion criteria and not violating exclusion criteria were randomly selected from a 2590 schizophrenia patient database. Patients were segregated into two groupings based on the Tirat Carmel criteria for Paranoid Schizophrenia (TCPS). Paranoid schizophrenia, hallucinatory subgroup (Subgroup H): Patients had a least one hallucinatory episode that lasted for more than a month within five years of illness onset. Paranoid schizophrenia, delusional subgroup (Subgroup D): Patients diagnosed with schizophrenia that did not fulfill criteria for the first group. Score results of Clinical Global Impression (CGI), Positive and Negative Syndrome Scale, (PANSS-8), Psychosocial Remission in Schizophrenia Scale (PSRS), and Quality of Life Enjoyment and Satisfaction Questionnaire 18 (QLES-Q-18) scales were compared between TCPS patient groups. Results: Subgroup H patients had significantly higher scores in positive and negative symptom categories of PANSS, as well as higher scores in all of the PSRS score categories, compared with Subgroup D patients. Over half of the QLES-Q-18 scores were significantly higher in Subgroup H patients compared with Subgroup D patients.

Conclusion: We found strong corroboratory evidence between TCPS groups and accepted psychiatric evaluation scales, suggesting the existence of paranoid schizophrenia subgroups.

Keywords: Delusions• Hallucinations• Paranoid schizophrenia• Tirat carmel criteria for paranoid schizophrenia patient subtypes

Introduction

Classic subtypes of schizophrenia in the DSM were eliminated in 2013 with the release of the 5th revised edition (DSM-5). The main intent behind discarding the subcategory descriptions was that schizophrenia is a spectrum disorder and that discrete categories do not adequately reflect the complex range of the illness. Some researchers have argued that schizophrenia subtype category stability over time was lacking and that, since the severity and progression of different psychopathological domains is highly individual, the usefulness of sub categorization of schizophrenia is a moot point [1,2]. Indeed, several studies have failed to demonstrate validity for any of the previously-used subgroupings in schizophrenia (paranoid schizophrenia, disorganized schizophrenia, undifferentiated schizophrenia) [3,4]. However, there are still clinical opinions that schizophrenia disorder is a heterogeneous grouping, and may consist of different subgroups. We should emphasize that we have examined only one subgroup, out of all the classic subgroups of schizophrenia; thus, this claim applies only to the group of patients with paranoid schizophrenia.

In our previous study [5], we demonstrated that paranoid schizophrenia subgroups do exist, which argues against their dismissal from the DSM-5. That study was an examination of patients with schizophrenia, who were discharged from the hospital and at the time of the study were in hostels transitional and/or permanent housing. Here, we have selected patients whose mental state was sufficiently stable and allowed them to function reasonably well outside of a residential facility. The results presented here demonstrate two clearly distinguished subcategories of patients and apply the same criteria as we used previously, now termed the Tirat Carmel criteria for paranoid schizophrenia patient subtypes (TCPS).

In an era of striving towards a personalized medicine approach to patient characterization and treatment, it follows that white-washing over a mental disorder by eliminating any refinement of resolution through elimination of subcategories works against the overall objective. Other authors have commented that the new DSM-5 classification, based on symptom clusters, is not fundamentally better than the prior subtype-based classification approach and further assert that its clinical utility has yet to be demonstrated [6]. Traditionally critical signs and symptoms of schizophrenia are not included with the recently adopted diagnostic criteria, which require further validation and are felt by some clinicians to not accurately characterize the disorder [7].

As we show in the present study by application of the TCPS to patient histories, there clearly exist identifiable subgroups of paranoid schizophrenia patients (delusional and hallucinatory). Further, additional corroboration through differentiation of said schizophrenia subgroups by psychiatric evaluation scales confirms their existence. In the present study,

***Corresponding Author:** Anatoly Kreinin, Maale Carmel Mental Health Center, Israel Institute of Technology, Haifa, Israel, Tel: +972-52-3903337; E-mail: kranata@gmail.com*

***Copyright:** © 2021 Kreinin A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.*

Received 28 January, 2021; **Accepted** 11 February, 2021; **Published** 18 February, 2021

our main goal was to verify that our data obtained in the previous study were replicable and that our findings were valid. Moreover, in contrast to the previous study, we tested patients after hospitalization. The second task was to we sought to verify our assertion that within the spectrum of schizophrenia disorders, among patients with paranoid schizophrenia there are at least two sufficiently homogeneous subgroups with distinctive clinical and epidemiological characteristics.

Materials and Methods

Study inclusion/exclusion criteria

The study was approved by the Maale Carmel Mental Health Center Institutional Review Board (02/18). Patients were recruited from 2018 to 2019 after providing written informed consent for participation in the study. Enrollment of patients was based on the following criteria:

Inclusion Criteria: Male and female outpatients between the ages of 18 and 75 who were clinically diagnosed with schizophrenia paranoid type according to the DSM-IV criteria. Patients must be capable of understanding the study goals and providing informed consent.

Exclusion Criteria: Patients incapable of providing informed consent or patients lacking capacity for consent based on the judgment of the treating psychiatrist.

Patient selection omiand evaluation

A database of 2590 schizophrenia patients from Maale Carmel Mental Health Center was reviewed for individuals who met inclusion criteria and did not violate exclusion criteria. Using a randomization program (www.randomizer.org), a set of 200 psychiatric outpatients was identified as the study base; from there, a subset of 100 patient participants was randomly selected. The choice in limiting the study patient numbers to 100 was based on constructing a sample set of equal size to our previous study of hostel schizophrenia patients and to replicate the methodology [5]. In the event that patients dropped from the study, new subjects were recruited from the 200-patient set through random selection. Potential participants were interviewed by an investigator to obtain information regarding age of onset of illness, suicide attempts, criminal behavior, and family status prior to onset of illness, psychoactive substance abuse, and number and duration of hospitalizations. Additional vital patient data was obtained directly from medical records. Study participants were evaluated by a board-certified psychiatrist through a structured clinical interview following DSM-IV-TR criteria for schizophrenia disorder and abuse/dependence on psychoactive substances. All patients in the study received standard psychiatric care and medications, including first- and second-generation antipsychotics at clinically-appropriate doses. No notable differences were observed with respect to patient treatment approach or administered medications. Assessment of psychiatric condition regarding mental state, presentation of positive and negative symptoms, and overall quality of life evaluation was measured using the following scales:

CGI: Clinical Global Impression [8].

PANSS-8: Positive and Negative Syndrome Scale [9], eight item symptom inventory [10].

PSRS: Psychosocial Remission in Schizophrenia Scale [11].

Q-LES-Q-18: Quality of Life Enjoyment and Satisfaction Questionnaire 18 [12].

Patient volunteers were subcategorized as either hallucinatory schizophrenia or delusional schizophrenia subtypes using the Tirat (Maale) Carmel criteria for paranoid schizophrenia patient subtypes (TCPS) [5], as follows:

1. Paranoid schizophrenia, hallucinatory subgroup (Subgroup H): Patients had a least one auditory hallucinatory episode that lasted for more than one month during the first five years since the onset of the disorder. In this group, the primary reason for hospitalization was the presence of hallucinations.

2. Paranoid schizophrenia, delusional subgroup (Subgroup D): Patients had a least one delusional episode that lasted for more than a month during first the first five years since the onset of the disorder. In this group, the primary reason for hospitalization was the presence of delusions.

The five-year window from illness onset was selected based on reported establishment of symptom stability within this timeframe, as noted in Kaplan and Sadock [13] and reported in a recent study by Hafner [14].

Statistical analysis

The cohort group consisted of people with a diagnosis of primary schizophrenia of more than 5 years of evolution. Those people with comorbidities, with health conditions or injuries that prevented postural control tests, with a diagnosis of secondary schizophrenia and with moderate or severe cognitive disabilities were excluded. The control group was healthy PTP, matched by sex and age with respect to the PWS group.

Procedure and instruments

All statistical analyses were performed with Prism 7.0 (GraphPad Software, San Diego, CA, USA). Analysis of study results was performed by Student's t-test for parametric data and Mann-Whitney U test or chi-square test for categorical data (α=0.05, two-tailed, all tests).

Age: Age groupings were arranged by accepted cutoff values for life stages according to Balsis et al. [15] and Debast et al., [16], who defined life stages as young adult (18-34), middle-aged adult (35-59), and older adult (60+).

Education: elementary (grades one through eight), high school (grades nine through twelve), higher education (any post-high school education).

Marital state: single (never married), married, divorced/widowed (binned to create a loss of spouse category and to meet statistical rules for contingency tables).

Age at diagnosis: Age groupings for binning were arranged as noted above (see Age), with the inclusion of juvenile (ages 8-17).

Duration of Disorder and Number of Hospitalizations: Binning was arranged based on simple decadal bins.

Results

The training courses

Among study participants, there were no significant differences between hallucinatory and delusional subgroups using the TCPS with respect to mean age, sex ratio, marital status, heredity of psychiatric disorder, smoking, mean age at first psychiatric diagnosis, mean duration of psychiatric disorder, or mean number of hospitalizations (Table 1). Education analyzed by stratification into elementary, high school, and higher education did not indicate any differences between H and D groups, however when mean years of education were analyzed, group D patients tended to have approximately 0.8 years more education than group H patients (p=0.045). In each subgroup, the number of male patients was notably higher (2.6 ± 0.2-fold). Differences between numbers of men and women in each schizophrenia subgroup was not significant (p>0.05).

Scorings in PANSS, PSRS, and Q-LES-18 suggested agreement with the TCPS in distinguishing differences between subgroups with respect to score value distributions (Table 2). CGI scores, a clinician-rated index that considers illness severity, global change in patient condition, and therapeutic response, were higher in group H patients compared with group D patients (4.52 vs. 3.93, respectively; p=0.014).

History Data		Hallucinatory	Delusional	Statistic	p
Age	Mean ± SE	41.5 ± 1.8	42.7 ± 1.7	t(98)=0.4883	0.6264
Sex	Male	39	33	X2(1)=0.0722	0.7822
	Female	16	12		
Education	Elementary	3	2	X2(2)=2.454	0.2932
	High School	47	34	t(98)=2.03	0.0450
	Higher Education	5	9		
	Mean years ± SE	11.2 ± 0.2	12.0 ± 0.4		
Marital State	Single	44	32	X2(2)=3.899	0.1424
	Married	3	8		
	Divorced/Widowed	8	5		
Heredity	Yes	34	21	X2(2)=2.793	0.2475
	No	5	8		
	Unknown	16	16		
Smoking	Yes	45	35	X2(1)=0.2525	0.6153
	No	10	10		
Age at Diagnosis	8-17	10	8	X2(2)=0.1940	0.9076
	18-34	37	29	t(98)=0.7523	0.4537
	35-59	8	8		
	Mean ± SE	24.3 ± 1.2	25.6 ± 1.2		
Duration of	1-10	17	13	X2(4)=3.030	0.5528
Disorder (Years)	11-20	20	20	t(98)=0.2282	0.8200
	21-30	13	7		
	31-40	2	4		
	40+	3	1		
	Mean ± SE	17.6 ± 1.4	17.1 ± 1.5		
Number of	0	2	3	X2(3)=0.7850	0.8531
Hospitalizations	1-10	38	31	t(98)=1.122	0.2646
	11-20	11	9		
	21+	4	2		
	Mean ± SE	8.9 ± 1.0	7.2 ± 1.1		

Data were analyzed by chi-square analysis and/or Student's t-test and represent mean values (±SE).

Table 1. Patient history information.

In the PSRS scoring system, all measures were able to distinguish between hallucinatory and delusional schizophrenia subgroups, as suggested by chi-square analysis of score distributions (Table 2). Hallucinatory schizophrenia patients, compared with delusional schizophrenia patients, tended to present with more impaired (means of hallucinatory vs. delusion subtypes): Q1. Familial relations (3.04 vs. 2.36), Q2. Understanding and self-awareness (4.15 vs. 3.13), Q3. energy level (3.53 vs. 2.80), Q4. interest in daily life activities (3.31 vs. 2.47), F1. self-care (3.16 vs. 2.53), F2. activism (2.86 vs. 2.24), F3. responsibility for medical treatments (4.35 vs. 3.47). No differences were observed between groups for PSRS F4. Use of community services (2.16 vs. 2.13). As a single assessment tool, the PSRS appears to characterize dissimilarity between hallucinatory and delusional subgroups.

Comparing PANSS scorings of hallucinatory and delusional schizophrenia subgroups indicated significant differences in all examined indices with exception to PANSS P1 score (Table 2). Hallucinatory subtypes tended to present with (means of hallucinatory vs. delusion subtypes): P2. Greater conceptual disorganization (3.06 vs. 1.96), P3. greater hallucinatory behavior (2.71 vs. 1.16), N1. More pronounced blunted affect (4.16 vs. 2.98), N4. greater passive/apathetic social withdrawal (3.82 vs. 2.73), N6. greater lack of spontaneity and flow of conversation (2.86 vs. 1.91), G5. Mannerisms and posturing (2.24 vs. 1.58), and G9. unusual thought content (2.64 vs. 2.09).

In the Q-LES-18 scorings, scores differed between hallucinatory and delusional patient subgroups in all indices except in items Q1-Q3, Q5, Q6, and Q15 (Table 2). Hallucinatory schizophrenia patients presented with lower average scores across the board compared with delusional schizophrenia subgroup patients (means of hallucinatory vs. delusion subtypes): Q4. Felt full of pep and vitality? (3.42 vs. 3.48), Q7. Felt able to communicate with others? (3.47 vs. 3.93), Q8. Felt able to travel about to get things done when needed? (3.47 vs. 3.80), Q9. Felt able to take care of yourself? (3.64 vs. 4.04), Q10. How often did you enjoy leisure time activities? (3.42 vs. 3.78), Q11. How often did you concentrate on the leisure activities and pay attention to them? (3.44 vs. 4.04), Q12. If a problem arose in your leisure activities, how often did you solve it or deal with it without undue stress? (3.15 vs. 3.96), Q13. Looked forward to getting together with friends or relatives? (3.22 vs. 3.60), Q14. Enjoyed talking with co-workers or neighbors? (3.20 vs. 3.76), Q16. Joked or laughed with other people? (3.42 vs. 3.80), Q17. Felt you met the needs of friends or relatives? (3.42 vs. 3.73), and Q18. Taking your medications? (3.49 vs. 4.31).

				Hallucinatory			Delusional
Measure	U	p		Mean	SE	Mean	SE
CGI	897.5	0.0140	*	4.51	0.15	3.93	0.17
PANSS P1	1206.0	0.8194		2.09	0.18	1.96	0.17
PANSS P2	632.0	<0.0001	**	3.05	0.17	1.96	0.15
PANSS P3	424.5	<0.0001	**	2.71	0.20	1.16	0.08
PANSS N1	525.0	<0.0001	**	4.16	0.13	2.98	0.18
PANSS N4	618.0	<0.0001	**	3.82	0.13	2.73	0.16
PANSS N6	691.5	<0.0001	**	2.86	0.17	1.91	0.15
PANSS G5	910.5	0.0152	*	2.24	0.19	1.58	0.11
PANSS G9	939.0	0.0314	*	2.64	0.17	2.09	0.15
PSRS Q1	855.0	0.0044	*	3.04	0.17	2.36	0.12
PSRS Q2	690.0	<0.0001	**	4.15	0.15	3.13	0.17
PSRS Q3	743.0	0.0002	*	3.53	0.12	2.80	0.14
PSRS Q4	708.0	<0.0001	**	3.31	0.14	2.47	0.13
PSRS F1	842.5	0.0035	*	3.16	0.13	2.53	0.13
PSRS F2	704.0	<0.0001	**	2.85	0.09	2.24	0.11
PSRS F3	778.5	0.0009	*	4.35	0.18	3.47	0.18
PSRS F4	1197.0	0.7532		2.16	0.09	2.13	0.10
QLES Q1	974.5	0.0540		3.51	0.19	3.87	0.13
QLES Q2	1042.0	0.1594		3.47	0.15	3.76	0.16
QLES Q3	1016.0	0.1096		3.62	0.13	3.91	0.15
QLES Q4	962.5	0.0465	*	3.42	0.13	3.78	0.15
QLES Q5	1055.0	0.1858		3.58	0.13	3.80	0.15
QLES Q6	1071.0	0.2203		3.56	0.11	3.78	0.14
QLES Q7	857.5	0.0053	*	3.47	0.12	3.93	0.12
QLES Q8	967.5	0.0482	*	3.47	0.13	3.80	0.13
QLES Q9	854.0	0.0045	*	3.64	0.09	4.04	0.15
QLES Q10	927.0	0.0231	*	3.42	0.12	3.78	0.12
QLES Q11	775.5	0.0006	*	3.44	0.12	4.04	0.13
QLES Q12	655.5	<0.0001	**	3.15	0.13	3.96	0.13
QLES Q13	913.5	0.0157	*	3.22	0.13	3.60	0.12
QLES Q14	864.5	0.0062	*	3.20	0.14	3.76	0.14
QLES Q15	1031.0	0.1337		3.47	0.13	3.73	0.14
QLES Q16	890.5	0.0103	*	3.42	0.10	3.80	0.15
QLES Q17	928.0	0.0217	*	3.42	0.11	3.73	0.14
QLES Q18	659.0	<0.0001	**	3.49	0.13	4.31	0.14

numbers [n]: hallucinatory, 55; delusional, 45)

Table 1. Rating scale metric differences between hallucinatory and delusional schizophrenia subgroup schizophrenia patients.

Discussion

The approach to characterization of schizophrenia has continued to evolve since the early days of the psychiatric discipline. In 1887 Kraepelin equated hebephrenia with dementia praecox (schizophrenia) and differentiated this state from catatonia and dementia paranoides (14). As a result, a section on mental disorders was included for the first time in the International Classification of Diseases (ICD-6) in 1949. The American Psychiatric Association also undertook an initiative in 1949 to standardize the diagnostic system throughout the United States. The result was the Diagnostic and Statistical Manual of Mental Disorders (DSM-I) in 1952. The classification was influenced by the theories of Adolf Meyer, where psychiatric disorders were viewed as reactions of the personality to psychological, social, and biological factors (15). Subsequently, DSM II was influenced by Bleulerian "4 A" criteria for diagnosis of schizophrenia. The DSM-II was published in 1968, but did not differ significantly from its predecessor.

The DSM-III was published in 1980 and marked a major change in the classification system. The result was a clearer definition of schizophrenia and the adoption of its division into subtypes. Until 2013, five subtypes were included in the DSM-IV-TR, which were: Paranoid type (DSM code 295.3/ ICD code F20.0); Disorganized type (hebephrenic schizophrenia in the ICD) (DSM code 295.2/ICD code F20.2); Undifferentiated type (DSM code 295.9/ ICD code F20.3); Residual type (DSM code 295.6/ICD code F20.5). The ICD-10 defines additional subtypes: Post-schizophrenic depression (ICD code F20.4); Simple schizophrenia (ICD code F20.6); Other schizophrenia including cenesthopathic schizophrenia and schizophreniform disorder NOS (not otherwise specified). (ICD code F20.8).

From DSM III up to the latest edition (DSM-5), the same argument has been made that a patient's subtype of schizophrenia can change throughout the course of the illness. Despite this understanding, no attempt prior to the DSM-5 was made to eliminate subtype descriptions. The five subtypes have been subsequently removed in the DSM-5 as the position of the American Psychiatric Association is that subtype descriptions lack clinical utility. Schizophrenia is now regarded as a spectrum disorder, with which we do not disagree. However, we did not find any evidence-based clinicoepidemiological studies published between 1980 and today that support the above findings of the American Psychiatric Association, especially regarding the paranoid subtype. It should be noted that the authors of the Comprehensive Textbook of Psychiatry themselves state, in

relation to the paranoid form of schizophrenia, that: "The paranoid subtype appears to have greater stability than the other subtypes and is used more often in clinical practice along with the undifferentiated type" [13].

We did not find any epidemiological, prospective, evidence-based, research that supports this weighty and far-reaching argument. We also did not find one prospective epidemiologic study that tests a hypothesis or claim that patients with, for example, paranoid schizophrenia change their symptoms and start to suffer from catatonia or become patients with disorganized or free of positive symptoms (simple) of schizophrenia. Furthermore, we believe that passing the same patient from one subgroup of schizophrenia to another is much more dependent on pre-hospitalization diagnosis in the Emergency Department (Unit), which is usually performed by a resident in psychiatry (not yet a specialist in psychiatry) who may lack experience in accurately diagnosing a psychotic condition. In addition, patients are diagnosed during different hospitalizations by different residents, which does not really contribute to "inter-rater reliability". It is clear to us that our hypothesis also requires testing and prospective multi-participant research.

The lack of support for traditional schizophrenia subgroupings should therefore not be taken as evidence that there exist no subtypes, rather that the subtypes used previously cannot be substantiated. Helmes and colleagues [3] undertook a cluster analysis approach with data from a small group of patients (107; similar to our study size of 100) and found no significant clustering among 55 schizophrenia symptoms examined. Korver-Nieberg and colleagues [4] conducted a larger study with 1064 patients, examining a variety of vital data and psychiatric items, including number of psychotic episodes and recent onset of psychosis. The researchers did not find any significant subgroups in their analysis either, however they elected to lump psychotic episode types under one heading and did not differentiate between delusional and more severe hallucinatory types.

A more recent study by Chen and colleagues examined over 1500 schizophrenia patients in datasets with PANSS scoring and conducted a machine-learning-based analysis using fuzzy c-clustering which was able to identify two distinct patient subtypes within the dataset [17]. Subtype A patients presented mostly with increased negative and affective symptoms, whereas subtype B patients presented with prominently positive symptoms and displayed an overall increased symptom severity. For patient records where functional MRI imaging data was available, strong correlations were also found between symptom severity, subtype, and alterations in brain function by resting-state functional connectivity (rsFC) analysis. Over 580 patients were clinically reexamined within several years of the collected assessment data listed in the dataset and symptom subtype classifications were reported as very stable in approximately 80% of the patients. Regarding the subtypes of Chen et al., who analyzed patient data across the schizophrenia spectrum and beyond the specific paranoid schizophrenia patients we examined here, our results suggest that subgroup H patients, and perhaps subgroup D patients as well, fall into their subtype B classification based on high positive symptomology. Additional recent evidence for subtypes within schizophrenia has been presented by researchers who have reported distinct metabolic [18,19], neuroanatomical [20], and cognitive [21] subgroups within the disorder spectrum. These findings further suggest that distinct subtypes of schizophrenia do indeed exist.

Despite elimination of traditional subcategory characterizations of schizophrenia through the DSM, the most recent International Classification of Diseases system (ICD-11) continues to retain more discrete descriptions of schizophrenia [22]. Regardless, there is much evidence to support dismissal of traditional schizophrenia nosology (reviewed in [23]). However, the ICD-11 classification mainly focuses on the periodic nature of schizophrenic episodes, whereas the TCPS differentiates between patients with schizophrenia based upon both timecourse of hallucinatory episodes and their frequency.

In this study, we selected to examine only outpatient patients with paranoid schizophrenia who were clinically evaluated and not identified in emergency department settings. In our experience, hostel patients have more stable symptom presentation, as we observed in our previous study which exclusively examined a cohort of this group [5]. In examining outpatients alone, we found that several prior results of significance differed when this outpatient group was considered. In addition, QLES-18 score patterns differed in significance between hostel (our previous study) and outpatients with schizophrenia.

We chose to apply a very simple set of criteria (TCPS) to differentiate between paranoid schizophrenia patients: those experiencing month-long or greater hallucinations within 5 years of illness onset (Subgroup H) and in this group, the primary reason for hospitalization was the presence of hallucinations versus those paranoid schizophrenia patients who either did not experience hallucinations or whose time course of hallucinatory experiences was shorter (Subgroup D) and in this group, the primary reason for hospitalization was the presence of delusions. After subdividing schizophrenia patients by these criteria, we found that several symptom inventories (PANSS, Q-LES-Q-18, and PSRS) yielded scoring distributions that mirrored a differentiation between the arranged subgroups.

Some corroboratory evidence in support of our findings does exist in the literature. Schwarz and colleagues recently reported finding two different subgroups among schizophrenia patients with respect to blood-borne immune factors, growth factors, and hormones [24]. Additionally, they observed a trend, albeit not significant, toward higher PANSS positive symptom scores in the DSM-IV subgroup with the greatest molecular changes. Similarly, we observed higher PANSS positive and negative symptom scores in the TCPS hallucinatory subgroup (Subgroup H). The Schwarz study group was small (180 schizophrenia patients) and the authors examined a broad set of metabolomic parameters, however alterations in neurophysiological patterns were not and could not be examined, which may be the missing pieces of the puzzle that would yield stronger clustering of subgroups and stronger PANSS score correlations. Here, we posit that the TCPS subgroups we examined may also present with markedly differing metabolomic profiles if examined. We propose this as a future course of investigation.

We believe the presence of these subcategories alone warrants additional investigation in order to continue to search for a source of clinical variability in subgroups in the schizophrenia group and to determine whether these groupings lead to differing prognoses and different treatment tactics and strategies for improved patient care. For example, it is clear that when dealing with the hallucinatory subgroup of the paranoid form of schizophrenia, the answer to the question of the need for clozapine in the early stages is unambiguously positive, as well as the unambiguously positive answer about the need to use various types of rehabilitation programs in the very early stages of the disease.

Summarizing the results obtained in this study, we can conclude that paranoid schizophrenia is indeed a distinct form of schizophrenia, which has clear characteristics that differentiate it from other forms of schizophrenia. In addition, we were able to replicate the results of the previous study and confirm the presence of additional significant differences between two subgroups of the paranoid form of schizophrenia – subgroup H with the predominant hallucinatory component and the subgroup D with the predominant delusional component. As in our previous study, we found that the hallucinatory subgroup tended to present with more impaired familial relations, understanding and self-awareness, energy level, interest in daily life activities, self-care, activism, responsibility for medical treatments, and use of community services. These results once again confirm the hypothesis that patients with strong hallucinations have greater impairment in comparison to patients with delusions, who retain a thought process. The disease process in patients with predominant hallucinations in their clinical picture is more destructive and begins earlier than among patients with predominant delusions" [25]. These results suggest that the most recent concept of schizophrenia patient subcategories, at least regarding a paranoid subtype, needs to be re-examined.

We acknowledge the limitations of this study in both the patient numbers, which were small, and that we noted no distinct differences between participating patients with respect to therapeutic approach or medications administered. All patients received reasonable doses of antipsychotics and were usually treated with a combination of first- and second-generation antipsychotic agents. Additional studies should be conducted with larger patient populations to determine whether there exist differences between schizophrenia subgroups regarding medication response, tolerance, and treatment progress.

Conclusion

In our two studies, we showed that the paranoid form of schizophrenia has clear clinical and epidemiological characteristics and that the paranoid form itself is divided into two subgroups that have significant differences. Thus, it becomes possible to further study this type of schizophrenia with sufficiently homogeneous subgroups, which may facilitate the search for possible genetic markers underlying this disorder.

References

1. Mattila, Taina, Maarten Koeter, Tamar Wohlfarth, Jitschak Storosum, et al. “Impact of DSM-5 Changes on the Diagnosis and Acute Treatment of Schizophrenia.” *Schizophr Bull* 41(2015): 637-643.
2. Carpenter, William T, and Rajiv Tandon. “Psychotic disorders in DSM-5: summary of changes.” *Asian J Psychiatr* 6(2013): 266-268.
3. Helmes E, Landmark J. “Subtypes of Schizophrenia: A Cluster Analytic Approach.” *Can J Psychiatry* 48(2003): 702-708.
4. Korver-Nieberg, Nikie, Piotr J Quee, Heleen B Boos, Claudia J Simons, et al. “The Validity of the Dsm-Iv Diagnostic Classification System of Non-Affective Psychoses.” *Aust N Z J Psychiatry* 45(2011): 1061-1068.
5. Kreinin, Anatoly, Vladimir Krishtul, Zvi Kirsh, and Michael Menuchin. “Clinico-Epidemiological Comparison of Delusion-Prominent and Hallucination-Prominent Clinical Subgroups of Paranoid Schizophrenia.” *Clin Schizophr Relat Psychoses* 9(2015): 117-124.
6. Farooq, Saeed, Ofer Agid, George Foussias, and Gary Remington. “Using treatment response to subtype schizophrenia: proposal for a new paradigm in classification.” *Schizophr Bull* 39(2013): 1169-1172.
7. Kendler, Kenneth S. “Phenomenology of Schizophrenia and the Representativeness of Modern Diagnostic Criteria.” *JAMA Psychiatry* 73(2016): 1082-1092.
8. Guy W Ecdeu. “Assessment Manual for Psychopharmacology” Department of Health E, and Welfare, editor. Rockville, National Institute of Mental Health (1976).
9. Kay, Stanley R, Abraham Fiszbein, and Lewis A Opler. “The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia.” *Schizophr Bull* 13(1987): 261-276.
10. Andreasen, Nancy C, William T Carpenter Jr, John M Kane, Robert A Lasser, et al. “Remission in Schizophrenia: Proposed Criteria and Rationale for Consensus.” *Am J Psychiatry* 162(2005): 441-449.
11. Barak, Yoram, Avi Bleich, and Dov Aizenberg. “Psychosocial Remission in Schizophrenia: Developing a Clinician-Rated Scale.” *Compr Psychiatry* 51(2010): 94-98.
12. Ritsner M, Kurs R, Gibel A, Ratner Y, and Endicott J. “Validity of an Abbreviated Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-18) for Schizophrenia, Schizoaffective, and Mood Disorder Patients.” *Qual Life Res* 14(2005): 1693-703.
13. Sadock BJS, Alcott V, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 10 ed. Philadelphia: Wolters Kluwer; 2017.
14. Häfner, Heinz. “From Onset and Prodromal Stage to a Life-Long Course of Schizophrenia and Its Symptom Dimensions: How Sex, Age, and Other Risk Factors Influence Incidence and Course of Illness.” *Psychiatry J Apr* 2019(2019): 9804836.
15. Balsis, Steve, Marci EJ Gleason, Carol M Woods, and Thomas F Oltmanns. “An Item Response Theory Analysis of DSM-IV Personality Disorder Criteria across Younger and Older Age Groups.” *Psychol Aging* 22(2007): 171-185.
16. Debast, Inge, Gina Rossi, S. P. J. Van Alphen, and Els Pauwels, et al. “Age Neutrality of Categorically and Dimensionally Measured DSM-5 Section II Personality Disorder Symptoms.” *J Pers Assess* 97(2015): 321-329.
17. Chen, Ji, Kaustubh R. Patil, Susanne Weis, and Kang Sim, et al. “Neurobiological Divergence of the Positive and Negative Schizophrenia Subtypes Identified on a New Factor Structure of Psychopathology Using Non-negative Factorization: An International Machine Learning Study. *Biol Psychiatry* 87(2020): 282-293.
18. Chand, Ganesh B, Dominic B Dwyer, Guray Erus, and Aristeidis Sotiras, et al. “Two Distinct Neuroanatomical Subtypes of Schizophrenia Revealed using Machine Learning.” *Brain Mar* 143(2020): 1027-1038.
19. Chen, Jingchun, Travis Mize, Jain-Shing Wu, and Elliot Hong, et al. “Polygenic Risk Scores for Subtyping of Schizophrenia.” *Schizophr Res Treatment* 23(2020): 1638403.
20. Ho, New Fei, Benjamin JH Lee, Jordon XJ Tng, and Max ZY Lam, et al. “Corticolimbic Brain Anomalies Are Associated with Cognitive Subtypes in Psychosis: A longitudinal Study.” *Eur Psychiatry* 63(2020): e40.
21. Habtewold, Tesfa Dejenie, Lyan H. Rodijk, Edith J. Liemburg, Grigory Sidorenkov, et al. “A Systematic Review And Narrative Synthesis Of Data-Driven Studies In Schizophrenia Symptoms And Cognitive Deficits.” *Transl Psychiatry* 10(2020): 244.
22. International Classification of Diseases for Mortality and Morbidity Statistics (11th Revision). *World Health Organization* (2018).
23. Braff, David L, James Ryan, Anthony J Rissling, and William T Carpenter. “Lack of Use In The Literature From The Last 20 Years Supports Dropping Traditional Schizophrenia Subtypes from DSM-5 and ICD-11.” *Schizophr Bull* 39(2013): 751-753.
24. Schwarz, Emanuel, Nico JM van Beveren, Jordan Ramsey, and F Markus Leweke, et al. “Identification of Subgroups of Schizophrenia Patients with Changes in Either Immune or Growth Factor and Hormonal Pathways.” *Schizophr Bull* 40(2014): 787-795.
25. Kreinin, Anatoly. “Hearing Voices" in Schizophrenia: Who's Voices are they?.” *Med Hypotheses* 80(2013): 352-356.

How to cite this article: Kreinin, Anatoly ,Mariia Ivenski, Dmitry Ivenski and Michael Kirby. “Clinico-Epidemiological Comparison of Delusion Prominent and Hallucination Prominent Clinical Subgroups of Paranoid Schizophrenia Outpatients.” *Clin Schizophr Relat Psychoses* 15s(2021). DOI: 10.3371/CSRP.IMKA.021221