Telomere Length as a Marker of Suicidal Risk in Schizophrenia

Длина теломер как маркер суицидального риска при шизофрении

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Original research

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ABSTRACT

BACKGROUND: Schizophrenia and suicidal behavior are associated with shortening in the length of telomeres. The aim of the study was to compare the content (pg/mcg) of telomeric repeat in DNA isolated from peripheral blood cells in three groups of subjects: patients with schizophrenia and a history of suicide attempts, patients with schizophrenia without suicidal tendencies, and healthy control volunteers.

METHODS: Relapses according to gender and age were examined in 47 patients with schizophrenia with suicidal behavior, 47 patients without self-destructive conditions, and 47 volunteers with healthy control and maintenance for the content of telomeric and the number of copies of mitochondrial DNA (mtDNA) in peripheral blood leukocytes.

RESULTS: Analysis of determining the content of telomeric repeat (TR) in the DNA of massive weight gain in the series: patients with schizophrenia and suicidal attempts — patients with schizophrenia without suicidal observations — healthy controls (225±28.4 (227 [190; 250]) vs. 243±21 (245 [228; 260]) vs. 255±17.9 (255 [242; 266]), p <0.005. The same trend is observed for the number of mtDNA copies (257±101.5 (250 [194; 297])) vs. 262.3±59.3 (254 [217; 312]) vs. 272±79.9 (274 [213; 304]); p=0.012), but no significant differences were recorded.

CONCLUSIONS: For the first time, the phenomenon of telomere shortening was discovered in schizophrenics with suicidal risk. The length of the telomere corresponds to the parameter of a biological marker — an objectively measured indicator of normal or pathological processes, but gaining an idea of its reliability is still necessary for verification with an assessment of its sensitivity, specificity, and positive and negative predictive value. The telomere may be considered a putative predictive indicator of suicidal risk.

АННОТАЦИЯ

ВВЕДЕНИЕ: Шизофрения и суицидальное поведение сопряжены с укорочением длины теломер. Целью исследования стало сравнение содержания (пг/мкг) теломерного повтора в ДНК, выделенной из клеток периферической крови, у трех групп испытуемых: пациентов с шизофренией и суицидами в анамнезе, пациентов с шизофренией без суицидов и добровольцев из числа здорового контроля.

МЕТОДЫ: Обследованы сопоставимые по полу и возрасту 47 пациентов с шизофренией с суицидальным поведением, 47 больных без аутодеструктивных тенденций и 47 добровольцев здорового контроля клинически и на предмет содержания теломерного повтора в ДНК лейкоцитов крови.

РЕЗУЛЬТАТЫ: Анализ определения содержания теломерного повтора (TR) в ДНК свидетельствует о статистически значимом увеличении длины теломер в ряду: пациенты с шизофренией и суицидами — пациенты с шизофренией без суицидов — здоровый контроль (225 vs 224 vs 255; *p*=0,024). Такой же тренд прослеживается для концентрации митохондриальной ДНК (мтДНК) (257 vs 262 vs 272; *p*=0,012).

ВЫВОДЫ: Впервые установили феномен укорочения длины теломер при шизофрении, сопряженной с суицидальным риском. Длина теломер отвечает параметрам биологического маркера — объективно измеряемого показателя нормальных или патологических процессов, но его валидность еще необходимо проверить с оценкой его чувствительности, специфичности, положительной и отрицательной прогностической ценности. Рассматривать длину теломер как прогностический индикатор суицидального риска преждевременно.

Keywords: *schizophrenia; suicide; telomere length; mtDNA*
Ключевые слова: *шизофрения; суицид; длина теломер; мтДНК*

INTRODUCTION

When publishing the study methodology and results, we should note two important features of schizophrenia, which are hardly comparable in terms of the universal human values of the 21st century, but are relevant separately, especially in light of the active search for biomarkers in psychiatric disorders and the development of contemporary approaches to reduce the risk of adverse outcomes in schizophrenia.

On the one hand, real-world psychiatric clinical practice shows that self-destructive behavior is a major cause of premature death among patients with schizophrenia. The suicide rate among patients with schizophrenia is 5–10 times higher than in the general population [1–4], and 25–50% of schizophrenia patients will attempt suicide during their life time, with 5.6% of suicide attempts ultimately proving fatal [5]. The mean age of schizophrenic patients who commit suicide is just 33 years, which is 10 years lower than in the general population [6–8], and completed suicide accounts for 30.9% of deaths during the first-episode psychosis [9–12]. Comparison of suicidal risk indices between the different nosologic groups shows poor results: the proportion of patients with schizophrenia can constitute 45–65% of suicidal patients with all other established psychiatric disorders [13, 14], and the lifetime rate of suicide in individuals with schizophrenia is between 9% and 13% [12, 15].

Meanwhile, the scientific literature discusses the hypothesis of accelerated aging due to oxidative stress and chronic neuroinflammation as a cause of schizophrenia [16–19]. According to this hypothesis, the oxidative stress associated with schizophrenia leads to premature degradation of cells and tissues, and endocrine and humoral abnormalities. All these factors, along with multiple decompensations, may lead to death 10–15 years earlier than otherwise expected [17, 20, 21][1].

Telomeres (TR), which are repetitive non-coding nucleotide sequences at the ends of the linear chromosomes (TTAGGG)n coated with binding proteins, are considered to be a 'biological counter' of the cell division number. Telomere shortening is directly and reliably associated with aging. A critical telomer length triggers the process of programmed cell death, which is accelerated in chronic cardiovascular disorders, metabolic syndrome, diabetes mellitus, and psychiatric disorders [24]. Telomere length homeostasis is achieved via a balance between the telomer erosion over successive eukaryotic cell divisions and telomere lengthening via telomerase, which adds repetitive nucleotide sequences to the 3' end of the DNA strand [24]. Oxidative stress is a major cause of direct telomere shortening. It has been established that 8-oxo-7,8-dihydro-2'-deoxyguanosine, a product of guanosine oxidation via hydroxyl radicals, is formed in larger amounts in a telomeric DNA sequence than in a non-telomeric DNA sequence [25].

[1] Other factors associated with schizophrenia may lead to abnormalities, e.g. higher smoking rates among patients with schizophrenia than in general population [22], poor quality of healthcare [23].

The length of the telomeres is defined by their content in the total DNA volume.

Mitochondrial DNA (mtDNA) copy number variation is considered to be a tandem marker for assessing the function of the 'biological counter' of telomere shortening. This marker reflects mitochondrial dysfunction, i.e., loss of reserve energy-generating capacity, especially in settings such as stress and psychiatric disorders [26–28].

Mitochondria not only provide the cell with necessary energy reserves, but also play a key role in the processes of apoptotic and necrotic cell death, regulation of gene expression, and the signaling pathways of cell proliferation and differentiation [29]. Mitochondrial biogenesis, determined by mtDNA copy number, may serve to compensate for increased energy demand or decreased mitochondrial function and is associated with aging and age-related diseases [30]. Several groups of researchers reported reduced leukocyte and whole blood mtDNA copy number in patients with psychiatric disorders, compared to healthy controls [31–34].

An analysis of publications on telomere shortening in schizophrenia and suicide reveals certain features. Controversial data[2] on telomere length in schizophrenia relative to healthy controls has been reported in the literature, but the results of meta-analyses [19, 41] demonstrate a significant telomer shortening in young patients with schizophrenia spectrum disorders [42]. These results were replicated in a tandem (combined) analysis of the telomere content and leukocyte mtDNA copies in young and middle-aged individuals [43, 44]. More significant correlation was observed in groups of patients with signs of psychiatric or developmental disorders [45].

The results of the studies on the telomer length and mtDNA in suicidal individuals without schizophrenia are sustained and reproducible. Comparison of samples obtained from 528 suicidal individuals and 560 subjects who died from other causes demonstrated significant telomer shortening in the brain tissue and blood cells [46]. Analysis of completed suicide cases showed shorter telomeres in female/young suicides and higher mtDNA content in male/elderly suicides [46]. These results were confirmed by comparison of telomere length in 71 suicidal individuals [47], which leads to the conclusion that telomere length is inversely associated with the risk of suicide in patients younger than 50 years old, including those with affective disorders [48].

As there are no available data on telomere length comparisons in suicidal patients with schizophrenia, we **hypothesized** that telomeres are shorter in patients with schizophrenia and a history of suicidal behavior relative to patients with schizophrenia without self-destructive behavior or healthy controls.

The aim of the study was to compare the content (pg/μg) of the telomeric repeats and the mtDNA copy number in the genome of peripheral blood cells in three groups of subjects: patients with schizophrenia and a history of suicidal behavior, patients with schizophrenia without suicidal tendencies, and healthy volunteers.

MATERIALS AND METHODS

The study population includes 94 patients with schizophrenia (55 males, 39 females, mean age 27.3± 8.6 years) who were admitted to the acute pathology units of the SBHI 'Psychiatric Clinical Hospital No.1 of the Moscow Healthcare Department' from February to March 2019.

Inclusion criteria

The patient's condition on evaluation meets the ICD-10 diagnostic criteria for schizophrenia; the patient has signed the Informed Consent Form.

Non-inclusion criteria

Severe decompensated somatic disorder; signs of psychoactive substance or alcohol abuse; pregnancy; refusal to participate.

To confirm the proposed hypothesis three groups of patients were formed based on the presence of suicidal behavior:

- group 1 (*n*=47, mean age 25±6.6 years, 30 males (64%)): patients with schizophrenia and a history of at least one suicide attempt;
- group 2 (*n*=47, mean age 29.5±9.8 years, 25 males (53%)): patients with schizophrenia without a history of suicidal ideation or behavior;
- control group (*n*=47, mean age 26±3.9 years, 22 males (47%)): healthy subjects without signs of psychiatric disorders and non-relatives of patients.

Study design: non-interventional, cross-sectional, case-control study.

[2] A number of studies have reported [21, 35, 36] an association between telomere shortening and schizophrenia, but these data have not been confirmed in other studies that have demonstrated longer telomeres in patients with schizophrenia [37], or no differences between these patients and healthy controls [38–40].

Methods

Clinical and psychometric approaches were used to assess the patient's condition and analyze their history. The Positive and Negative Syndrome Scale (PANSS) was used to evaluate the patient's condition, taking into account the Positive (PANSS P), Negative (PANSS N) and General Psychopathology (PANSS G) subscale scores [49].

Blood sampling from the cubital vein was performed once at 8.00 to 8.30 a.m. after overnight fasting; samples were drawn into heparin tubes and sent to the laboratory within two hours in compliance with requirements regarding biomaterial preservation.

Molecular biology method was used to measure the telomere and mtDNA content in samples obtained from patients in three study groups.

The result of telomere content measurement was expressed as pg/μg of DNA, and the result of mtDNA content measurement was expressed as the copy number in the genome.

We used the quantitative non-radioactive hybridization (NQH) assay, specially designed for the quantitative analysis of tandem repeats in the genome. The NQH method has been detailed in several publications [50–52]. DNA was isolated from blood by extraction with organic solvents. The DNA concentration in the solution was measured via fluorimetry using PicoGreen dye (Invitrogene). The NQH method is based on the hybridization of denatured DNA samples applied to a filter (50 ng/spot) with a biotinylated DNA probe that is complementary to the DNA fragment of interest. The biotin-(TTAGGG)7 oligonucleotide (Sintol, Russia) was used as a DNA probe. The streptavidin-alkaline-phosphatase conjugate (Sigma) was used to detect biotin after hybridization. Alkaline phosphatase substrates (BCIP/NBT) in the presence of the enzyme form an insoluble precipitate, which is adsorbed on the filter at the DNA target location. When the reaction ends, the filter is scanned and integral intensity (I) of the spots is determined using a special program. Several DNA calibration standards with a known TR content are applied to the same filter. The calibration dependence relates the signal (I) to the number of repeats in 50 ng of DNA. An example of a calibration dependence for telomeres is given in one of our previous publications [53]. The standard error of the NQH method is 5% of the measured value. The total error of the method, which includes DNA isolation, determination of the DNA concentration in solution, and hybridization, is 11%.

Assay for mtDNA quantification

Quantitative PCR assay (RT-PCR) was used to analyze the mtDNA copy number in DNA. The methodology and primers for mtDNA analysis are described in detail in the publication [53].

Statistical data analysis was carried out using the Jamovi software (The Jamovi Project (2022)). jamovi. (Version 2.3) [Computer Software], https://www.jamovi.org.). Descriptive statistics include medians and quartiles. T-test with indication of the degrees of freedom (df), t-test parameter (t) and a 95% confidence interval (95% CI) were used for analysis of the psychometric scale scores, as well as clinical and dynamic characteristics. The Mann-Whitney test (U-test) with the calculation of all test parameters was used to compare the molecular testing results in gender groups. The Kruskal-Wallis test was used for statistical analysis of group data via continuous variables, and the Dwass, Steel, Critchlow-Fligner test (DSCF pairwise comparison) was used to test paired hypotheses. Correlation between variables was assessed using Pearson's χ^2 test. For all tests, data were considered statistically significant at a two-sided p <0.05.

RESULTS

The results of clinical, psychometric, and molecular testing are presented in Tables 1, 2, 3, and 4.

The groups were matched for gender, although the number of men in group 1 (patients with suicide attempts) was higher than in the control group — 64% vs. 47%), however, this difference was not statistically significant.

The vast majority of patients in each of the groups have impaired social functioning and live reclusive lives (the proportion of single patients was 80.9% in the study population, and 87.3 and 74.5% in the respective groups) and are persistently disabled in some cases (the proportion of disabled persons was 15% in the study population, and 13 and 17% in the respective groups). Analysis of environmental factors affecting telomere content and mtDNA copy number (smoking and metabolic syndrome) did not reveal significant differences between the groups (Table 1).

Clinical and dynamic characteristics of two groups were heterogeneous (Table 2).

Group 2 patients were significantly older than group 1 patients and the healthy controls.

Table 1. Socio-demographic characteristics and description of factors affecting the telomere length and cfDNA concentration in the study groups

Characteristics	Group 1 *n*=47	Group 2 *n*=47	χ^2 (*p*)	Control *n*=47	χ^2 (*p*1)	χ^2 (*p*2)
Socio-demographic characteristics, abs. (%)						
Males	30 (64%)	25 (53%)	1.096 (0.3)	22 (47%)	2.755 (0.1)	0.383 (0.5)
Single	41 (87.3%)	35 (74.5%)	2.474 (0.1)	27 (57.4%)	10.421 **(0.001)** *	3.032 (0.1)
Disabled	6 (13%)	8 (17%)	0.336 (0.6)	0	-	-
Telomer shortening risk factors, abs. (%)						
Smoking	13 (27.6%)	7 (14.8%)	2.287 (0.1)	8 (17%)	1.533 (0.2)	0.079 (0.8)
Metabolic syndrome	4 (8.5%)	4 (8.5%)	0 (1)	3 (6%)	0.111 (0.7)	0.111 (0.7)

Note: p — differences between the study groups; *p*1 — differences between the control group and the group of patients with schizophrenia and a history of at least one suicide attempt; *p*2 — differences between the control group and the group of patients with schizophrenia without a history of suicidal ideation or behavior; * — statistically significant difference when using Chi-Squared test.

Table 2. Clinical and dynamic characteristics of schizophrenia in study groups

Value	Group 1 *n*=47	Group 2 *n*=47		Control *n*=47		
	Years±SD	Years±SD	*p* (df) (t) [95% CI]	Years±SD	*p*1 (df) (t) [95% CI]	*p*2 (df) (t) [95% CI]
Mean age	25±6.6	29.5±9.8	0,010* (92) (2.6) [7.9–1.1]	26±3.9	0.404 (92) (0.8) [3.2–1.3]	0,023* (92) (2.3) [0.5–6.6]
Mean age at onset	18.7±6.5	19.1±6	0.743 (92) (0.3) [3–2.1]	-	-	-
Disease duration	6.3±6.0	10.4±8.5	0,008* (92) (2.7) [7.1–1.1]	-	-	-
Mean AP dose, mg/day**	400±27.3	300±19.5	< 0.001* (92) (20.5) [90.7–110]	-	-	-

Note: p — differences between the study groups; *p*1 — differences between the control group and the group of patients with schizophrenia and a history of at least one suicide attempt; *p*2 — differences between the control group and the group of patients with schizophrenia without a history of suicidal ideation or behavior; * — statistically significant difference when using the t-test; **AP — antipsychotic chlorpromazine equivalents [54].

Further, in both groups the onset of schizophrenia was found to begin during late puberty or adolescence (18.7±6.5 vs. 19.1±6; *p*=0.74), and therefore the disease duration is significantly shorter in patients with suicide attempts than in patients without suicidal ideation (6.3±6.0 vs 10.4±8.5; *p*=0.0083). Moreover, the statistically significant difference in antipsychotic dosage should be noted: group 1 patients receive more intensive treatment (400±27 vs. 300±20 mg/day of chlorpromazine equivalent; *p* <0.0001).

Table 3 shows the results of psychometric testing in the two groups of patients: statistically significant differences were found in the severity of negative symptoms, as measured by the PANSS-N subscale mean score (27.4 vs 22.8 points; *p*=0.0052), while no differences were found in the total score or Positive and General Psychopathology subscale scores.

Results of telomere content measurement (Table 4) show a statistically significant difference in telomere length between the three groups (*p* <0.001; χ^2=24.8; df=2). DSCF pairwise comparisons revealed significant differences in telomere length between some groups. Statistically significant differences in telomere content were found

Table 3. Results of psychometric testing in the study groups

Scale	Group 1 *n*=47 Total score mean±SD (Me [Q1; Q3])	Group 2 *n*=47 Total score mean±SD (Me [Q1; Q3])	*p* (df) (t) [95% CI]
PANSS total score	101.2±23.1 (97 [86; 112])	94.9±26.3 (94 [76; 112])	0.223 (92) (1.2) [3.9–16.4]
PANSS P	23.8±7.6 (23 [18; 27])	24.9±8.5 (23 [20; 29])	0.522 (92) (0.6) [4.4–2.2]
PANSS N	27.4±8.8 (26 [22; 33])	22.8±6.6 (11 [19; 28])	**0.005*** (92) (2.9) [1.4–7.8]
PANSS G	50±10.9 (49 [44; 59])	47.2±15.3 (48 [39; 59])	0.318 (92) (1) [2.7–8.2]

Note: * — Statistically significant difference when using the t-test.

Table 4. Molecular testing results

Biomarker concentrations	Group 1 *n*=47 Total score mean±SD (Me [Q1; Q3])	Group 2 *n*=47 Total score mean±SD (Me [Q1; Q3])	Control *n*=47 Total score mean±SD (Me [Q1; Q3])	*p** (χ^{2}*) (df*)
Telomers (pg/mcg DNA)	225±28.4 (227 [190; 250])	243±21 (245 [228; 260])	255±17.9 (255 [242; 266])	< 0.001** (24.8) (2)
mtDNA (copy number)	257±101.5 (250 [194; 297])	262.3±59.3 (254 [217; 312])	272±79.9 (274 [213; 304])	0.579 (1.09) (2)

* — The Kruskal-Wallis test was used for the analysis, the statistics for which are given in parentheses: χ^{2} — chi-squared; df — degrees of freedom.

** — The Kruskal-Wallis test revealed a statistically significant difference in the three study groups. The BSCF test was used for pairwise comparison, and a significant difference in telomere content was found between group 1 and group 2, group 1 and the control group, and group 2 and the control group.

between the group of patients with a history of suicide attempts and the group of patients without suicidal ideation (225 pg/mcg±28.4 (227 [190; 250]) vs. 243 pg/mcg± 21 (245 [228; 260]); *p*=0.007; W=2.3). Statistically significant differences in telomere content were found between the group of patients with a history of suicide attempts and the control group (225 pg/mcg±28.4 (227 [190; 250]) vs. 255 pg/mcg±17.9 (255 [242; 266]); *p* <0.001; W=6.7) and between the group of patients without suicidal ideation and healthy controls (243 pg/mcg±21 (245 [228; 260]) vs. 255 pg/mcg±17.9 (255 [242; 266]); *p*=0.041; W=3.4). There were no significant differences in mtDNA copy number between the three study groups (*p*=0.579; χ^{2}=1.09; df=2).

Comparison of the telomere and mtDNA content in male patients (Table 5) shows statistically significant differences: the telomer content was significantly lower in males with a history of suicide attempts compared to those without suicidal ideation (216±27.1 (208 [193; 242]) vs. 240.9±25.7 (250 [219; 260]); *p*=0.002, U-test=198), while the mtDNA content was reduced without statistically significant differences. Amongst women, there were no statistically significant differences in the telomere and mtDNA content between the two groups.

DISCUSSION

Before the discussion of the results, we would like to emphasize that the significant telomere shortening demonstrated in our study cannot serve as definitive biological evidence of completed suicide predetermination in patients with schizophrenia, even though other studies

Table 5. Molecular testing results by gender

Biomarker concentrations in male patients in the two study groups			
Data	**Group 1 Males (*n*=30) Total score mean±SD (Me [Q1; Q3])**	**Group 2 Males (*n*=26) Total score mean±SD (Me [Q1; Q3])**	***p* (Mann-Whitney U) (U-test) [95% CI]**
Telomers (pg/mcg DNA)	216±27.1 (208 [193; 242])	240.9±25.7 (250 [219; 260])	0.002* (198) [43–10]
mtDNA (copy number)	246±104.1 (252 [158; 289])	280±61 (255 [244; 255])	0.130 (298) [85–6]
Biomarker concentrations in female patients in the two study groups			
Data	**Group 1 Female (*n*=17) Total score mean±SD (Me [Q1; Q3])**	**Group 2 Female (*n*=21) Total score mean±SD (Me [Q1; Q3])**	***p* (Mann-Whitney U) (U-test) [95% CI]**
Telomers (pg/mcg DNA)	241±24 (249 [227; 253])	245±15 (245 [233; 254])	0.692 (165) [15–10]
mtDNA (copy number)	276±97 (234 [226; 339])]	277±66 (254 [225; 318])	0.837 (171) [55–38]

Note: * — Statistically significant difference when using the U-test.

demonstrate telomere shortening and a decrease in the mtDN copy number in the cells of postmortem specimens from suicide completers compared with those who died from other causes [46].

Clinical assessment of risk of suicide in schizophrenia is based on the identification of symptomatic, environmental, and behavioral factors such as gender, age, history of suicide attempts, family history of suicides, etc. A meta-analysis has shown that the risk of suicide is highest in young men with a history of suicide attempts and a poor compliance with psychopharmacotherapy [55]. According to the literature, clinical and dynamic risk factors of suicide in schizophrenia are the signs of an unfavorable disease course (early disease onset with frequent relapses and hospitalizations, need for high-dose antipsychotics [56–59] and long-term psychiatric hospitalization [60–62]), which are associated with the negative symptom severity and social maladaptation [63], and which may lead to telomere shortening to a greater extent [64].

In this study, we identified the risk factors of unfavorable course of schizophrenia in both groups, but their significance in terms of risk of suicide cannot be considered reliable. Thus, male patients are predominant in the study population, but this parameter is statistically insignificant (64% vs. 53%; p=0.3). Patients with a history of suicide attempts were younger at the onset of schizophrenia, but the difference in this parameter was not statistically significant (18.7±6.5 vs. 19.1±6.0 years; p=0.74). Meanwhile, in the group of patients with a history of suicide attempts, statistically significant differences in the PANSS-N score — a measure of negative symptom severity associated with an unfavorable course of schizophrenia — was observed (27.4±8.8 (26 [22; 33]) vs. 22.8±6.6 (11 [19; 28]) points; p=0.0052). According to the literature, this parameter can be directly correlated with reduced telomere and mtDNA content [65].

Significant differences in disease duration were found; however, disease duration was shorter in patients with a history of suicide attempts (6.3 vs. 10.4 years; p=0.0083), that is, the more prominent telomere shortening in this group compared to the patients without suicidal ideation can be explained not only by the course of psychiatric disorder, but by a combination of several factors, which is consistent with the results of telomere evaluation at different stages of schizophrenia [65].

First, antipsychotic agents provide active telomerase expression via transcription factor 4 (TCF4) activation in the presence of protein kinase-B (alpha serine/threonine-protein kinase, Protein kinase B alpha, Akt1) and glycogen synthase-3-β-catenin (glycogen synthase kinase GSK3β) that block type 2 dopamine and/or serotonin receptors [66]. In schizophrenia, GSK3β is activated and Akt1 is inhibited both in the cells of the cerebral cortex and the blood [67], and this is can be directly correlated

with TCF4 deactivation and telomere shortening [64]. Antipsychotics increase serine phosphorylation of GSK3β [68] and block both D2- and 5-HT2A receptors, thus increasing telomerase synthesis, which, in turn, leads to telomere shortening. In this study, patients with a history of suicide attempts received antipsychotics in typical therapeutic doses (400 mg/day vs. 300 mg/day of chlorpromazine equivalent; p >0.05), which could lead to telomer shortening. On the other hand, treatment response is an important predictor of telomere length, and there is some evidence that therapy-resistant patients have shorter telomeres compared to healthy individuals and patients in remission [69, 70]. It has been found that many antipsychotics, including clozapine, risperidone, haloperidol, olanzapine, and chlorpromazine, may inhibit the respiratory chain and cause mitochondrial damage by increasing oxidative stress [71], which may also explain the reduced mtDNA content, as shown in a similar study [28].

Secondly, factors exacerbating the consequences of oxidative stress [72], such as smoking [35, 37, 38, 40, 70] and metabolic syndrome as a pro-inflammatory process [73], cause telomere shortening. There was no statistically significant difference in the number of smokers and patients with metabolic syndrome between all groups, hence the difference in telomere and mtDNA content may be a coincidence and not a trend, as shown in a number of studies [74].

Although our results partially reproduce the literature data, it must be reiterated that the causes of telomere shortening in schizophrenia or suicide may be different. In addition to the natural telomere shortening with each cell division, oxidative stress, and chronic inflammation play a significant role [75]. It seems more likely that the reduction in telomere content and mtDNA copy number may be the result of cumulative exposure to the chronic stress associated with schizophrenia [76].

CONCLUSIONS

In this study, we, for the first time, identified the phenomenon of telomere shortening in schizophrenia associated with suicidal risk. However, we emphasize that it would be premature to consider telomere length a prognostic indicator of risk of suicide. Undoubtedly, telomere length has all features of a biomarker, i.e., objectively measured index of normal or abnormal processes, but its validity still needs to be verified through an assessment of its sensitivity, specificity, and positive and negative predictive value. An analysis of the factors affecting telomere length (smoking, metabolic disorders, antipsychotic therapy) in the study participants does not demonstrate a direct relationship between telomere shortening and risk of suicide amongst those with schizophrenia.

The study limitations were relatively small sample size and failure to account for additional factors that affect the qualitative characteristics of the studied markers. The latter include, for example, gender differences in suicidal behavior or the father's age at conception [40, 77, 78]. The telomere content and mtDNA copy number in the nucleus of peripheral blood leukocytes may differ from those in other tissues (for example, neurons) due to the fact that antipsychotics reduce telomerase expression in leukocytes [64].

It seems promising to search for possible protective factors (for example, telomerase inhibitors), which may act as triggers for the development of a specific therapy to reduce suicidal tendencies by slowing the rate of telomer shortening. However, identification of such trends may contribute to the development of alternative agents that will reduce the impact of oxidative stress and slow telomere shortening within this patient population.

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