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Clinical Investigation

Precision Medicine and Schizophrenia: What about Telomere Length?

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Abstract

Introduction: Precision Medicine is a concept dependent on a deeper understanding of the individual and his illness. The understanding of schizophrenic disease stands on categorical classifications which exclude the disease's ethiological and pathogenic features. Telomeric dysfunction, a way of measuring accelerated ageing, has been associated with some diseases. The purpose of this paper is to understand the relationship between telomere size and schizophrenia, and to infer if it can be used in Precision Medicine.

Materials and methods: We searched for scientific articles using Medline database, via Pubmed and ISI Web . We used the he following terms: schizophrenia, precision medicine, psychiatry, pathogeny, ethiology, telomere, cross-sectional studies. After an exclusion process, 51 articles were analysed.

Results: Most of the analysed articles are cross-sectional. The evidence is inconsistent. There are articles that claim that telomere length decreases, others do not find statistically significant differences and others advocate an increase in telomere length in schizophrenia. Several arguments are listed for these results.

Discussion: The conflicting results seem to be mainly explained by the limitations of cross-sectional studies. Further longitudinal studies are proposed. Furthermore, such results can also be explained by the multifactorial nature of schizophrenia.

Conclusion: Because Precision Medicine needs advanced and detailed data, and the study of telomeres in schizophrenia isn't reproducible, its usefulness in this disease remains uncertain.

Keywords

Precision medicine; Personalized medicine; Individualized medicine; Schizophrenia spectrum and other psychotic disorders; Schizophrenia; Telomere; Telomere shortening

Abbreviations

TL: Telomere Length; ICD-10: International Classification of Diseases 10th Revision; DSM-5: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; SNP: Single nucleotide polymorphism

Introduction

Precision Medicine is a concept that is not new but needs a deeper understanding and further exploration. In

today's clinical practice, the classical ''signs and symptoms'' approach is typically used [1], relying on a population-based knowledge that grounds evidence-based medicine [2]. The aim of Precision Medicine is to incorporate individual variability in genes, environment, and lifestyle into strategies of prevention, diagnosis, and treatment that take these individual features into account [2]. We witnessed a recent development of large-scale biologic databases [3]. The better understanding of all this data will allow the stratification of patients [1] in increasingly smaller subgroups with important traits that can be identified and hopefully influence those patients diagnosis, disease stratification, risk assessment and treatment.

Form Kraepelin's concept of dementia praecox, to the introduction of Schneider's first-order symptoms and to the ICD-10 and DSM-5 diagnostic criteria for schizophrenia [4], much has changed regarding the definition of this disease. There are some differences between the ICD-10 and DSM-5 classifications. Nonetheless, they also have many things in common. These classifications define clusters of patients according to certain clinical presentations [5]. However, it is increasingly clear that schizophrenia is a complex disease that can´t be easily defined. Some elements of its etiopathogenesis are known, but these are not yet included in the two major manuals of mental illness [6,7]. This categorical way of looking at mental illnesses, specifically for schizophrenia, contrasts with the pragmatic way that other medical-surgical specialties organize their knowledge [8].

Genetic factors, neurodevelopmental theories and neurotransmitters hypothesis have been suggested as possible explanations for the disease [4]. Electrophysiology [9], neuroimaging data and some environmental factors [10] have also been used to define schizophrenia. However, the exact pathological mechanisms behind schizophrenia remain unknown, [11] despite having numerous studies on the subject. It is now known that schizophrenia is a multifaceted and multifactorial complex brain disease. The difficulty in finding a causal link between risk factor - disease is due to the small weight of those risk factors by themselves [4,12]. This is a disease where genetic and environmental backgrounds interact to create the known clinical presentations [13].

Telomeres are a composite of DNA and proteins located at the end of chromosomes. They act as a cap, with the purpose of safeguarding chromosome stability. It is known that with successive cell divisions, the length of telomeres tends to shorten, attenuated by molecular mechanisms of repair. Simultaneously, they are complexes

susceptible to injury mechanisms that accentuate their shortening. These telomeric dysfunctions have been associated with age-related diseases: Immunodeficiencies, cardiovascular diseases, cancer or diabetes. It is speculated that this connection may be causal when interacting with other risk factors or may be the result of the pathophysiological consequences of a particular disease [14]. Schizophrenia is a disease with high mortality and morbidity. Thus, it is speculated that the aging process may be accelerated in this disease [15].

This review article aims to clarify the relationship between TL and Schizophrenia. Additionally, it is intended to illustrate if and how this association can be used in the assumptions of Precision Medicine.

Material and Methods

In order to carry out this review, we searched for scientific articles using the Medline database, via Pubmed and ISI Web of Knowledge. We selected the articles in English, French or Portuguese. We used the search terms: schizophrenia, precision medicine, psychiatry, pathogeny, ethiology, and telomere. Only articles in English and French were found. Based on the assumption that the articles were published between 1 January 2000 and 31 October 2018, 68 articles were selected based on their title. After reading the abstract, we excluded 31 articles and the remaining 37 were fully read. We read and included 15 further articles that were pulled from the bibliographic references of the aforementioned articles.

Results

Within the analysed studies on the topic of telomere in schizophrenia we found twenty-three cross-sectional studies (N=23), five meta-analyses (N=5) and a longitudinal study (N=1). The cross-sectional studies showed conflicting results regarding TL in schizophrenic individuals. There are articles saying that TL decreases [16-18], other articles do not find significant differences[19, 20] and some advocate an increase in TL. [21-23] Of the five meta-analysis, four of them conclude that TL is shortened in schizophrenic patients when compared to healthy controls [24-27]. Darrow et al., while seeking to establish a relationship between TL and various psychiatric disorders, concluded that the decrease in TL was only statistically significant for cases of depression and anxiety disorders. Nevertheless, the results were not statistically significant in schizophrenia [28].

Table 1, summarizes the results found in the cross-sectional studies. No quantitative measures were taken due to the wide variety of statistical analysis used in the selected studies.

Studying individuals at different stages of the disease has shown interesting results. Maurya et al. compared antipsychotic-naive patients (N=81) and chronic patients (N=173) with healthy controls (N=438). The author did not find a significant change in TL in patients with first schizophrenic episode compared to healthy controls. However, non-remitted schizophrenic patients had a significantly higher TL than remitted schizophrenic patients. The author proposes the effect of antipsychotics as an explanation. A chronic patient with more symptoms takes more medication which can influence telomeres, increasing their length. [22] The same author, in another cross-sectional study, demonstrated a decreased TL in individuals at high risk for psychosis compared to healthy controls. A possible explanation would be the absence of long-term influence of antipsychotic medication in those individuals [17]. Similar results were obtained by Cui et al. With the intention of comparing individuals with recent psychosis (N=43) and chronic psychosis (N=83), these authors concluded that TL would be increased in these two groups, also significantly, when compared to the group of healthy controls [29].

Larger lengths of telomeres in schizophrenics have been reported in other studies. Nieratschker et al. also reported that schizophrenic individuals would have higher TL [21]. Savolainen et al. went further, demonstrating that hospitalized and medicated psychiatric patients had higher TL than healthy out-of-hospital controls [30]. Nieratschker et al. sought to explain these results. First, accepting that reduced hippocampal volume and poor episodic memory are characteristics of schizophrenia, it might be that their finding (an increased TL) facilitates the bridge between these this feature and schizophrenia. Second, and similarly to what Savolainen et al. reported, antipsychotic drugs may have antioxidant effects preventing telomere abrasion. Third, they recall that advanced paternal age is related to higher TL in their offspring. Thus, TL might not be a cause of schizophrenia, but a marker of paternal age at the time of conception. Finally, they assume that their results may be biased by an increase in mortality in the schizophrenic psychiatric population [21,30]. In an attempt to explain this increase in TL in schizophrenic patients, Rao et al. reported the effect of antipsychotics on telomerase positive signalling pathways [26].

Although some studies have shown a connection between antipsychotics and TL, others have not reached the same conclusion [23, 31-33]. Riley et al. were unable to correlate TL with antipsychotic medication. Even though they took into account the antipsychotic medications taken at the time of the study, they argue that they

did not consider the cumulative exposure of the schizophrenic cases through the years [33]. Conversely, Zhang et al. calculated the lifetime dose of antipsychotics. In their study, they also found increased TL in schizophrenic patients but did not correlate this data with lifetime antipsychotic dose. They explain their results considering their population of cases: elderly Japanese patients with long hospitalizations. In fact, the authors associate long hospital stays in Japan with a practice of a healthy lifestyle promoted in those health institutions. Schizophrenic patients hospitalized for a long time will then be healthier and have a lower risk of metabolic syndrome [23]. Pawelczyk et al. studied 42 patients with early psychosis and 44 with chronic psychosis. They obtained the daily doses of chlorpromazine and converted them into equivalent doses of chlorpromazine. There was no association found between equivalent doses of chlorpromazine and TL [32].

Rao et al. found results in a meta-analysis that contradict the aforementioned data. They showed a non-statistically significant decrease in TL in medicated patients compared to controls. The naive and control antipsychotic groups were statistically the same. After the separation of the medicated patients into good responders and poor responders, only the group of poor responders showed a decrease in TL that did not prove to be statistically significant. In order to justify the result of the bad responders, the authors present the potential state of greater oxidative stress experienced by these patients [26]. Similarly, the relationship between TL and response to therapy was also addressed by Yu et al. These authors claim that treatment-resistant patients show a statistically significant decrease in TL. The reasoning behind this could again be an increased to oxidative stress and the subsequent cell damage [34]. In another meta-analysis by Lin et al. the authors showed that the disease stage is an important variable in the data analysis. The poor responders to antipsychotics and naive antipsychotic patients were those who showed statistically significant decreases in TL. The other medicated patients showed no differences in TL with the control group. Lin et al. defends that patients who are not responders to pharmacological therapy are the most severe patients. Therefore, they may be exposed to increased oxidative stress [24].

Instead of grouping patients into good responders or poor responders, Monroy et al. divided the schizophrenic patients according to the type of antipsychotic they took: typical or atypical. The group of patients receiving atypical antipsychotics was subsequently divided into groups according to the risk of metabolic syndrome

caused by those antipsychotics: high, medium or low. Only the patients taking high risk atypical antipsychotics presented a statistically significant decrease in TL compared to controls. These high-risk antipsychotics are described as having a high risk of metabolic syndrome [35].

Some authors have also explored the difference between sub-phenotypes of schizophrenia. Rao et al. in a cross-sectional study compared groups of patients with paranoid schizophrenia (N=52), with non-paranoid schizophrenia (N=89) and with healthy controls (N=120). The patients with paranoid schizophrenia had lower TL compared to the group with non-paranoid schizophrenia and to the control group [26]. The same author, in another study, found three single nucleotide polymorphisms at the TERT locus that would be associated with paranoid schizophrenia in the study population: rs2075786, rs4975605, and rs10069690. Only the SNP rs2075786 was shown to correlate with decreased TL. This might imply a role of telomerase reverse transcriptase polymorphisms in telomere erosion. However, TRT polymorphisms may increase the risk of schizophrenia by mechanisms other than TL [36]. Rao et al. recalled the correlation between the positive symptoms of paranoid schizophrenia (hallucinations and delusions) and the stressful events of childhood. The author also recalled that childhood traumatic events may be involved in the process of telomeres accelerated erosion [26],

Other authors have investigated the relationship between early exposure to traumatic situations and TL. Riley et al. studied schizophrenic cases (N=48) and comparative controls (N=18) reaching interesting conclusions. The two groups did not demonstrate statistically significant differences between TL and trauma indices. Performing a gender-specific analysis to find a correlation with early trauma, the authors reported the following results: only male patients and female controls showed reduced TL related to early trauma. The authors admitted that the results may have been random but advised the performance of sex stratification in the analysis of TL results. Nevertheless, they admitted that stress could lead to smaller TL by augmenting oxidative stress [33]. Xavier et al. studied a high risk group of children and adolescents living in families with high psychiatric burden (N = 1553) and a comparative control group (N=958) in an attempt to relate TL to childhood trauma. The male individuals with higher scores of infantile trauma had smaller TL, which wasn't the case with the female individuals. The two arguments that support these findings are: 1) the scientific evidence that women have larger

telomeres and 2) hormonal theories that claim that oestrogens can activate telomerase and that testosterone increases susceptibility to oxidative stress [37].

The acknowledgment that reduced TL is sex-specific was also discussed by Wolkowitz et al. Although their sample of patients was schizophrenic and schizoaffective (N = 134), when men and women were examined separately it was possible to verify that TL decreased faster in men than in women. Additionally, from the age of 48, women (control and schizophrenic) showed a greater TL than men (controls and schizophrenics) [38]. The opposite relation was found by Malaspina et al. When studying the association between advanced paternal age and TL, this author observed that TL was higher in male schizophrenic patients and TL was lower in female schizophrenic patients. In men, despite not considering TL a cause of the disease, the authors hypothesize that this higher TL is associated with the risk of disease through shared genetic susceptibility. In women, they consider the possibility of paternal X chromosome effects. There may be an abnormality in the X-linked epigenetic process [39].

Endophenotypes are laboratory quantitative markers [40] that are hereditary, trait-related (meaning that the endophenotype is always present during the evolution of the disease and is state-independent) and should be associated with a disease occurring in the population. In non-affected relatives of schizophrenic individuals, the prevalence of the endophenotype should be higher than in the general population [41,42]. In order to study the theory of accelerated aging through a potential endophenotype, Czepielewski et al. included schizophrenic individuals, their unaffected siblings and comparative controls. They measured TL in all groups and concluded that this measure did not differ between schizophrenic patients and their siblings. In comparison with the control group, the schizophrenic group had lower TL [43].

Most studies measure TL in peripherical leukocytes [22, 23,37]. However, there is a strong correlation between TL measured in leukocytes and TL measured in other tissues [33]. Cui et al. measured TL in lymphocytes T. It is argued that these cells play an important role in the pathophysiology of the brain diseases since they often pass the blood-brain barrier. They produce pro-inflammatory cytokines [29]. Two articles investigated the TL in brain tissue but did not find correlations with the diagnosis of schizophrenia. Nevertheless, these studies focused on brain gray matter [44,45]. Van Mierlo et al. examined both white and gray brain areas, given that white areas

may be the ones that suffer the most from cellular insults. The authors proceeded to measure TL in white and gray brain tissue from upper temporal gyrus and medial frontal gyrus in patients with schizophrenia (N=9) and controls (N=11Similarly to the other two studies, they did not find significant differences in TL in cerebral gray matter. They found, however, a significant decrease of TL in the white matter of the upper temporal gyrus. To explain the results Van Mierlo et al. recalled diffusion tensor imaging studies that showed temporal white matter deficits in brains of schizophrenic patients [46].

Some studies have found a negative correlation between TL and age [21,38], while in others this relationship has not been demonstrated [29,37].

To date, there is a longitudinal study that compared TL in young individuals in a first psychotic episode (N=16) and in a healthy control group (N=21). In both groups, they calculated TL at an initial time and after 12 months of follow-up. At the beginning of the study, there were no differences in TL in the two groups. The same cannot be said after a year of follow-up: TL was significantly decreased in individuals with a first psychotic episode compared to the control group. The authors argue that this may be a sign of accelerated cellular aging in individuals with a first psychotic episode [47].

Discussion

Each author proposes reasonings that, individually, appear to be plausible justifications of their results. When gathering the information, we find that results are ambiguous. Moreover, the existence of a wide variety of study designs is a major limitation in drawing conclusions on this subject.

In fact, most of the analysed studies are cross sectional studies. This has implications in drawing conclusions about TL. The major limitation of in this study design is the difficulty in infering causal relations [48,49]. Rao et al. question whether a shortening of telomeres is causally involved in schizophrenia, or if this observation reflects the progression of the disease [26].

Another major limitation of cross-sectional studies is confounding, because the real relationship between a variable (in this case TL) and an outcome (in this case, schizophrenia) can’t be reliably assessed. In this case, if an association between variable and outcome is found, it can’t be ruled out that there are external factors influencing the variable and consequently the outcome [50]. Therefore, many authors mention that they were

unable to obtain detailed information on some confounding factors. In their meta-analysis, Polho et al. enunciate some confounding factors that may influence TL: Oxidative stress, use of antipsychotics, metabolic syndrome and cardiovascular diseases, smoking and paternal age [25].

In addition, the results of cross-sectional studies are collected and analysed at a single point in time [48]. Wolkowitz et al. acknowledged that based on cross-sectional data, they are unable to deduce whether any difference in TL was due to an accelerated aging process. They observe that this difference in TL could also result from an initial insult, probably genetic, with no subsequent changes in telomere with age [38].

Because evolution of TL is an intricate process occurring within a time frame, some authors recommend the use of longitudinal studies to evaluate the temporal dynamics that may occur in this process [18,27,38]. However longitudinal studies are difficult to perform since they require time, money and large samples.

The movement of TL measurement in brain tissue and not in peripheral leukocytes is encouraging. This allows for a stronger support of the causal relation in a given outcome. It has already been determined that the changes would be more relevant in cerebral white matter. In fact, neuroimaging studies conclude that anatomic-architectural alterations exist throughout the brain tissue, with the widening of the ventricles and frontotemporal dysfunction being more pronounced [51].

Finding a negative correlation between TL and age is important, since it is a universal demonstration that supports the robustness of the study and the correct measurement of TL in the study [21]. However, this observation, made in cross sectional studies can't fully prove the presence of accelerated aging in schizophrenia.

The effect of antipsychotics on TL is not clear. Current evidence is in disagreement, claiming that the use of these drugs may both increase or decrease TL. In fact, there is evidence that some antipsychotics may inhibit the release of nitric oxide in activated microglial cells, potentiating neurodegeneration processes in schizophrenia. On the other hand, there is growing evidence that these drugs may have antioxidative action by stimulating anti-inflammatory cytokines such as IL-4 or IL-10 [52].

Another possibility for these results may arise from the multifactorial nature of schizophrenia. At this point it cannot be said that TL, along with other etiological factors, is one of the contributors to the genesis of the disease. Nevertheless, it is easily understood that in a disease with multiple etiological factors, each with a

different weight to their contribution depending on the individual, these factors will have a diversity of effects on TL.

Conclusion

Speaking of Precision Medicine and assuming that TL will have an etiological involvement in schizophrenia, TL will not be the only diagnostic determinant of the disease. As a multifactorial disease, each biomarker found plays a minor role in the ethiology of the disease. All information collected on schizophrenia should be included in large databases, in order to reflect the heterogeneity of the disease, the inter-variability of the risk factors, and the magnitude of that risk, individually and together as well as the documented etiological factors. A technological map of this disease is necessary to realize how intricate it is and to facilitate new scientific questions and new investigative paths.

Because Precision Medicine must be based on solid data, and the study of telomeres in schizophrenia is not very reproducible, its usefulness in building a precise medicine in schizophrenia remains inconclusive. We believe that this is an innovative subject that still needs further investigation. This area is promising in terms of better phenotyping and achieving a closer knowledge of the biological substrate of pathology as heterogeneous as schizophrenia.

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Table 1: Cross Sectional Studies, summary of the evidence.

Study	Cases	Controls	TL in cases	Main observations
Maurya, 2018	Antipsychotic-naïve patients (N=81) and Chronic patients (N=173)	N=438	↑	↑ in non-remitted patients
Maurya, 2017	Individuals at high risk of psychosis (N=22)	N=88	↓	
Cui, 2017	Recent psychosis (N=43) and chronic psychosis (N=83) patients	N=35	↑	Lack of a correlation between age and TL
Nierastschker, 2013	Schizophrenic patients (N = 539)	N = 519	↑	Presence of a correlation between age and TL
Savolainen, 2012	Patients with a mental disorder (N=116)	N=1840	↑	Presence of a correlation between age and TL ↑ particularly in hospitalized and medicated patients
Zhang, 2018	Schizophrenic patients (N=1241)	N=1042	↑	Lack of a correlation between TL and lifetime antipsychotic dose
Riley, 2018	Schizophrenic patients (N=48)	N=18	≈	Association appeared with sex-stratification: only male schizophrenia cases and female healthy controls showed diminished TL in association with early trauma Lack of a correlation between antipsychotic medication and TL (although doses were not assessed)
Pawelczyk, 2015	Chronic psychosis patients (N=44)	Early psychosis patients (N=42)	↓	Association between the results and the phenotype of the disease (duration and severity of the disease)
Kao, 2008	Schizophrenic patients (N=31)	N=41	↓	Lack of an association between TL and duration of the disease, antipsychotic dose and age.
Yu, 2008	Schizophrenic patients: good (N=34) and poor (N=34) responders	N=76	↓	Presence of an association between TL and age. Association between TL and disease phenotype (particularly disease severity with ↓ TL in the poor responders patients)

Monroy-Jaramillo, 2017	Schizophrenic patients (N=170)	N=126	≈	Association found between antipsychotic regimen and TL: ↓ in patients under treatment with clozapine and olanzapine
Rao, 2016(a)	Paranoid schizophrenia (N=52) and non-paranoid patients (N=89)	N=120	↓	Association found between schizophrenia phenotype and TL: ↓ only in the paranoid subgroup, after dividing schizophrenic patients into two subgroups
Rao, 2016(b)	Paranoid schizophrenia (N=98)	N=109	↓	Presence of an association between TL and age ↓ in cases with the rs2075786 SNP
Xavier, 2018	Children and adolescents living in families with high psychiatric burden (N=1553)	N=958	↓	Lack of an association between TL and age, and between TL and sex ↓ particularly within male individuals with higher scores of infan5le trauma
Wolkowitz, 2017	Schizophrenic and schizoaffective patients (N=134)	N=123	≈	Diagnosis doesn't show an association with TL. Meanwhile sex is the major determinant of TL: ↓ particularly in male individuals (cases and controls)
Malaspina, 2014	Schizophrenic patients (N=53)	N=20	≈	Lack of an association with age. Association with paternal age and family history: ↑ male with older parents. Even more ↑ in males with older parents and family history
Czepielewski, 2016	Schizophrenic patients (N=36), unaffected siblings (N=36)	N=47	↓	Lack of an association with sex Presence of an association with age
Zhang, 2010	Schizophrenic patients (N=46)	N=48	≈	Observations only in gray matter
Van Mierlo, 2017	Schizophrenic patients (N=9)	N=9	↓	Observations only found in white matter
SNP: Single Nucleotide Polymorphism; ↑ : increased ↓ decreased; ≈ similar/without an association; TL: Telomere Length				