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Cognitive performance, symptom severity, and survival among patients with schizophrenia spectrum disorder: A prospective 15-year study

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ABSTRACT

Patients with schizophrenia have an average lifespan approximately 20 years shorter than the normal population. This study explored if there were any specific common characteristics among patients with schizophrenia spectrum disorder who died prematurely, compared to those who survived or died at a more normative age. The data were obtained from an ongoing twenty-year longitudinal study wherein 67 patients out of 501 participants had died at an average age of 60.5 years. Differences in baseline assessments of symptoms and cognitive ability were compared across patients who died during the time of the study and survivors. Symptom remission was assessed according to the Andreasen remission criteria as presented in 2005. Cognitive performance was assessed with a battery of instruments measuring vigilance, working memory, learning, short-term memory, and executive function. Two patients committed suicide and together they lowered the average lifespan of the study sample by only 0.27 years. The baseline assessments showed no difference in symptoms or remission status between patients who died and those who survived. This finding was in contrast to the cognitive baseline assessments where it was found that those who had died had performed more poorly in multiple domains, especially executive functioning, cognitive flexibility, learning and short-term memory. Survival analysis with Cox models showed that verbal memory and executive functioning were the most substantial independent predictors. Our study shows that although suicide was not a common cause of death, the average age of death is still young for this patient group and cannot be explained by differences in symptom severity. Our findings indicate that cognitive abilities might be of special interest for affective longevity in patients with schizophrenia, either as a marker of special risk or as a target for direct intervention.

1. Introduction

Patients with schizophrenia spectrum disorders have a shorter life expectancy compared with the general population. This knowledge is not new, and, in recent years, the focus on this issue has intensified thanks to several scientific studies (Brown et al., 2000; Lawrence et al., 2013). Moreover, research suggests that the difference between patients and Healthy Controls (HC) has been increasing rather than decreasing with added life expectancy in the healthy population (Nielsen et al., 2013; Saha et al., 2007). A number of studies investigated causes of death, such as chronic diseases (Crump et al., 2013; Osborn et al., 2007; Ifteni et al., 2014), suicide (Palmer et al., 2005; Sinyor et al., 2015), and metabolic side effects of antipsychotic treatment (Mitchell et al., 2013; Torniainen et al., 2015). Analyses have been based on data obtained from various cohorts, population- and cause of death-registers, and autopsy studies. The predominant causes of death found were sudden death from cardiovascular disease, as well as cancer, and suicide. Osborn et al. (2007) found an increased odds ratio of 3.22 for people under 50 with schizophrenia to die of coronary heart disease compared with the normal population; the corresponding risk for stroke was 2.53. In a British population of patients with schizophrenia, Brown et al. (2000) found a suicide rate of 18%, whereas Lawrence et al. (2013) found that in Western Australia 19.8% of the men and 7.1% of the women with schizophrenia committed suicide. However, in a meta-analysis of data from the United States, Europe, and Asia during 1966–2005, Palmer et al. (2005) found that the lifetime suicide prevalence for the group as a whole was 4.9%. Crump et al. (2013) and Torniainen et al. (2015) concluded that certain drug treatments had a protective effect against premature death. On the other hand, metabolic syndrome, including those caused by medication side effects, increases the risk of mortality (Torniainen et al., 2015). Also, cigarette smoking is correlated with impaired cognitive and adaptive abilities (Depp et al., 2015), and the risk of increased ill health (Stubbs et al., 2015). In all, patients with schizophrenia have a shortened life expectancy of

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more than 10 years (Tiihonen et al., 2009), or, according to Laursen et al. (2014), of approximately 20 years.

The main variation in methods across previous studies is information available on patients prior to the time of death. Most studies focus on patients' features assessed deaths retrospectively and related them to such as cause of death, age, comorbidity, and various risk factors. There have been few studies that systematically followed patients prospectively before death occurred. The consequence is that, in most studies, the knowledge regarding the patient is based solely on retrospectively collected data from medical records. Moreover, as the data contained in medical records are not based on standardized protocols, there are significant variations and differences in quality of data from patient to patient (Sedgwick, 2014) as well as minimal data on critical features such as cognitive performance that are not commonly collected in some clinical settings. Due to the lack of standardized approaches to the studying of this phenomenon, there is also a built-in risk of bias when various early signs of increased risk of premature death are analyzed (Sedgwick, 2012).

This prospective study, which followed patients for a long period prior to their death, examined whether any distinctive differences in symptoms or neurocognitive abilities predicted an increased risk of premature death. In this study, we examined the comparative predictive power of clinical symptoms, indexed by clinical severity and the proportion of cases experiencing extended clinical remission, as well as cognitive deficits. We have previously reported on both the clinical and cognitive features of this sample, finding that their characteristics on a cognitive performance basis were very consistent with those seen in a large sample of patients assessed with similar strategies in the United States (Harvey et al., 2009). Thus, despite the substantial differences in level of support and assistance provided in Sweden and the US, there was essentially no difference in cognitive performance or the ability to perform critical everyday skills.

2. Methods

This paper presents results from the Clinical Long-term Investigation of Psychosis in Sweden (CLIPS) study, which is a naturalistic follow-up of psychiatric outpatients. Participants are scheduled to be followed for up to 20 years from baseline, and a total of more than 500 patients with schizophrenic psychosis according to the DSM criteria have participated in the CLIPS study since it began in year 2000. Approximately two thirds of the potential participants in the geographic recruitment area, defined by healthcare catchment regions, were included. The study was approved by the Ethical Research Committee in Gothenburg, Sweden, and carried out in accordance with the latest version of the Helsinki Declaration.

2.1. Participants

The study followed 501 patients, 282 men and 219 women, of whom 67 patients were deceased as of year-end 2014. All patients were enrolled starting in the year 2000 with an average follow-up time of 9.5 years and with a standard deviation of 2.9 years. They were diagnosed with schizophrenia spectrum disorders such as schizophrenia (316, of whom 43 died), schizoaffective disorder (118, of whom 14 died) or delusional disorders (67, of whom 10 died). No difference in mortality was found between the diagnosis groups regarding distribution (Chi-square) or age (one-way ANOVAs, 5% level). The symptomatic remission rate was for the whole population 40.8%. Comorbidities, such as autism and mental retardation, were exclusion criteria for participation in the study.

2.2. Design

The 501 patients were divided into two groups: *surviving* and *dead* as of December 31, 2014. All patient data were compiled and then compared group-wise for symptoms and neurocognitive abilities at baseline (starting in 2000). Preliminary tests showed no significant differences in cognitive capacity between the three diagnostic groups: schizophrenia, schizoaffective disorder, and delusional disorder (one-way ANOVAs, 5% level). Hence, we did not use the diagnosis group classification in the analyses, as there were no differences in either the mortality outcomes or the predictors.

We divided the deceased cohort members into two separate subgroups to rule out the possibility that data from patients who died at a more normative age affected the results. Thus, one subgroup contained data from patients who died before the age of 70 while the other contained data from patients who died after the age of 70. Data was missing for some measurement instruments. The number of patients with data from the different tests is presented in conjunction with the results.

2.3. Symptom measures

All participants were assessed with either the *Positive and Negative Syndrome Scale* (PANSS; Kay et al., 1987) or the *Psychosis Evaluation Tool for Common use by Caregivers* (PECC) (De Hert et al., 2002; Lindström et al., 2012). Participants were interviewed using an adapted Swedish translation of the Structured Clinical Interview—Positive and Negative Syndrome Scale (SCI-PANSS) (Lindström et al., 1994). The patients' answers to the interview questions were the basis for the subsequent scoring, on a seven-step scale, for positive symptoms (7 items), negative symptoms (7 items), and general symptoms (16 items).

The PECC (De Hert et al., 2002) consists of a total of 20 items divided into five four-item domains: positive, negative, depressive, excitatory, and cognitive symptoms. The results were analyzed by summarizing the five domains and the total score. Over time, changes occurred in the study design, leading to a gradual transition from the PECC to the PANSS. Patients were initially assessed solely with the PECC, then with a combination of the PECC and the eight items included in the PANSS to determine the occurrence of remission, and, finally, with the complete PANSS instrument. In total, 363 patients were assessed with the PANSS. Remission was defined according to the Andreasen criteria (Andreasen et al., 2005; Lasser et al., 2007). This study presents the PANSS results when such assessments were available for the patient at the first or second assessment session and presents the PECC results for the remaining patients. When the PECC results of these remaining patients were compared with all patients that were assessed with the PECC at baseline there were no differences in total score or individual domains between the two groups based on survival.

A total of 122 patients had been assessed with the complete PECC. Sixteen patients lacked complete PECC scores and were excluded from analyzes of the relationship between symptoms and death. Twenty of the 122 patients assessed with the PECC died (16.4%). Regarding remission, 476 patients (of whom 60 died) were rated according to the Andreasen criteria.

2.4. Cognitive measures

A total of 295 patients participated wholly or partly in the neurocognitive assessments at baseline. Most patients ($n = 295$) completed Wechsler Adult Intelligence Scale—Vocabulary (WAIS-Vocabulary), while 223 patients completed the Continuous Performance Test—Identical Pairs (CPT-IP 450). This is the same sample of patients reported on, with the same tests, in Harvey et al. (2009). An analysis was performed to examine differences between patients who had performed the cognitive tests and those who had not. A Mann–Whitney U test did not show any significant differences between the two groups according to gender, age at first consultation in psychiatry or symptom severity, i.e. PANSS total score, PECC total score and remission status.

The *Continuous Performance Test—Identical Pairs* (CPT-IP 450) is a vigilance test that assesses the participant's ability to respond to a target

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