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A 15-year comparative follow-up study of adolescent schizophrenia and acute and transient psychotic disorders with onset in adolescence

15-letnie porównawcze badania katamnestyczne schizofrenii młodzieńczej oraz ostrych i przemijających zaburzeń psychotycznych z początkiem w okresie młodzieńczym

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Abstract

Aim: Comparative follow-up studies on the course of adolescent schizophrenia, on the one hand, and syndromes diagnosed initially as acute and transient psychotic disorders in adolescence, on the other, are rare in the literature. In our analysis, we compared the course of these syndromes based on selected clinical and social indicators. **Materials and methods:** A total of 34 patients hospitalised in adolescence (time point 1) for schizophrenia (11 patients) and for acute and transient psychotic disorders (23 patients – both diagnoses according to the ICD-10 criteria) were re-examined 15 years later (time point 2). The assessment was based on a psychiatric examination as well as questionnaires, letters and queries in selected hospitals and psychiatric wards. **Results:** After 15 years, the respondents in the group with a baseline diagnosis of schizophrenia revealed a significantly higher severity of schizophrenia symptoms, particularly the axial symptoms of the illness, as well as a higher severity of cognitive deficits. They had more frequent and longer psychiatric hospitalisations during the follow-up period, with the difference being more pronounced in the sub-period of the first five years after hospitalisation. These subjects experienced a deeper regression at time point 2, with lower levels of insight and poorer working lives, and were significantly more likely to receive a diagnosis of schizophrenia than patients in the other group. **Conclusions:** A diagnosis of adolescent schizophrenia proves to be a more significant predictor of the patients' deteriorated functioning both in terms of clinical and social parameters than a diagnosis of acute and transient psychotic disorders made during the same developmental period.

Keywords: schizophrenia, schizophrenia spectrum and other psychotic disorders, adolescence, prognosis

Streszczenie

Cel pracy: W literaturze przedmiotu rzadko spotyka się porównawcze badania katamnestyczne nad przebiegiem z jednej strony schizofrenii młodzieńczej, a z drugiej zespołów rozpoznawanych wyjściowo jako ostre i przemijające zaburzenia psychotyczne w okresie młodzieńczym. W niniejszej analizie autorzy porównują przebieg tych zespołów w oparciu o wybrane wskaźniki kliniczne i społeczne. **Materiał i metody:** 34 pacjentów hospitalizowanych w okresie dojrzewania (punkt 1) z powodu schizofrenii (11 osób) oraz z powodu ostrych i przemijających zaburzeń psychotycznych (23 osób – obie diagnozy wg kryteriów ICD-10) zostało powtórnie zbadanych 15 lat później (punkt 2). Oceny dokonywano w oparciu o badanie psychiatryczne, a także ankiety, listy oraz kwerendę w wybranych szpitalach i oddziałach psychiatrycznych. **Wyniki:** Badani z grupy z wyjściową diagnozą schizofrenii po 15 latach ujawnili znacząco wyższe nasilenie objawów schizofrenii, w szczególności osiowych objawów tej choroby, a także wyższe nasilenie deficytów poznawczych. Częściej i dłużej byli psychiatrycznie hospitalizowani w okresie katamnestycznym, przy czym różnica ta bardziej zaznaczała się w podokresie pierwszych 5 lat po hospitalizacji. Osoby te w punkcie 2 ujawniały głębszą regresję, niższy poziom wglądu, uboższe życie zawodowe oraz znacznie częściej niż badani z drugiej grupy uzyskiwali diagnozę schizofrenii. **Wnioski:** Diagnoza schizofrenii młodzieńczej jest rokowniczo znacznie bardziej obciążająca zarówno w obszarze parametrów klinicznych, jak i społecznych niż diagnoza ostrych i przemijających zaburzeń psychotycznych postawiona w tym samym okresie rozwojowym.

Słowa kluczowe: schizofrenia, spektrum schizofrenii i inne zaburzenia psychotyczne, adolescencja, rokowanie

INTRODUCTION

Despite the well-established knowledge of age-dependent differences in the presentation of schizophrenia, since the 1980s the disease has been diagnosed on the basis of uniform criteria, i.e. without taking into account the specificity of the developmental age. Only a small proportion of catamneses, which are an important component of research activity in the field of schizophrenia, includes the population of patients with schizophrenia diagnosed in childhood and adolescence (early-onset schizophrenia, EOS) or only childhood (very early-onset schizophrenia, VEOS). Adolescent schizophrenia, taken separately, is very rarely investigated catamnestically, even though it accounts for about 15% of all cases of the disease (Clark, 2006) and, due to the specificity of adolescence, requires a separate and particularly careful approach (e.g. Haddock et al., 2006; Häfner and Nowotny, 1995; Remschmidt, 2001). In contrast, the nosological status of the category of acute and transient psychotic disorders (ATPDs) is weaker and less precisely defined, while the clinical phenomenon itself is studied less frequently and in a less structured manner. However, it appears that the occurrence of volatile psychotic syndromes, which are difficult to describe precisely, is a common experience of most clinicians. In some cases, they are a harbinger of the development of schizophrenia or other processual psychoses. Sometimes they are reactive in nature or unveil clinically the psychotic tendencies present in a malformed personality. It also happens that over time a somatic or organic background to their development emerges. If such a syndrome occurs in adolescence, the adolescent crisis itself may undoubtedly be a contributory factor in the catalogue of causes. Although the evolution of the diagnosis of ATPDs towards schizophrenia is a frequent phenomenon, the pattern of disease course over time and the distant level of social functioning still clearly distinguish between populations with a baseline diagnosis of schizophrenia and ATPDs in favour of the latter diagnosis (Marneros et al., 2003). However, comparative follow-up studies are scarce, especially among patients with adolescent onset. We have found only two such studies, with only partially similar methodologies. One was conducted more than 20 years ago in Israel (Valevski et al., 2001) and the other 10 years ago in Warsaw (Remberk et al., 2014, 2012). Thus, we felt that it would be worthwhile to take up this research topic, especially considering the fact that the aforementioned Polish study showed that the prevalence of ATPDs against other psychoses might even be several times higher among adolescents than adult patients.

MATERIALS AND METHODS

The research project was conducted several years ago, in parallel with a more extensive 45-year follow-up of cases of adolescent schizophrenia, the results of which had already been published (Ślosarczyk et al., 2022a, 2022b, 2022c, 2022d). The study population consisted of patients treated in the inpatient adolescent psychiatric ward of the Department of Adult, Child and Adolescent Psychiatry in Kraków, who were hospitalised psychiatrically for the first time in their lives between 1999 and 2003 (time point 1) and were then discharged from the hospital with a diagnosis of adolescent schizophrenia (F20 according to ICD-10: 11 patients) or acute and transient psychotic disorders (F23 according to ICD-10: 23 patients). On average 15 years after that hospitalisation (2015–2017: time point 2), a re-examination was performed. An invitation to participate in the study – describing the course of the study and explaining the purpose – was sent to the living patients (to our knowledge, one person had died earlier) by registered letter. Those who, to the best of our knowledge, received the letter but did not respond were sent another registered letter with a follow-up questionnaire containing 11 questions on various aspects of follow-up functioning along with a request to complete it and return to the clinic in the enclosed return envelope. A total of 33 letters were sent, and 17 patients were examined in person (10 people with a baseline diagnosis of F23 and seven with a diagnosis of F20), most at the Department of Adult, Child and Adolescent Psychiatry, and some in their private homes and flats. For six people (four with a diagnosis of F23 and two with a diagnosis of F20), the questionnaires and letters were the sources of information. Independently, queries were carried out in 20 hospitals and psychiatric wards where, according to the highest probability, the interviewed persons might have been repeatedly hospitalised psychiatrically during the follow-up period. Data on time point 1 were obtained by analysing the medical records of the hospitalisation period. To process the collected data, the modified Turku Schizophrenia Assessment Form (TSAF) and Follow-up Assessment Form (FAF) sheets constructed in the 1960s by Alanen and Räkköläinen, also used in the aforementioned 45-year follow-up period, were implemented. Also, the Global Assessment of Functioning (GAF) scale from the DSM-IV-TR (American Psychiatric Association, 1995) was applied, and additional categories were created, as described later in this paper. The study had been approved by the Bioethics Committee, and the participants had given their written informed consent to participate in the study.

The psychopathology of schizophrenia recorded at time point 2 was divided into the following categories: *autism*, *apathy and abulia*, *splitting symptoms*, *formal thought disorder*, *catatonic symptoms*, *hebephrenic symptoms*, *delusions*, and *hallucinations*. The severity of each symptom was assessed by personal examination in a four-point ordinal scale. The sum of the schizophrenic psychopathology (*sum of schizophrenic symptoms*) was also calculated by adding together the severity determined in all eight symptom groups, and scores were summed for the most typically schizophrenic symptoms in the sense of the axial symptoms of schizophrenia proposed by Eugen Bleuler (*autism*, *apathy and abulia*, *splitting symptoms*, *formal thought disorders*), obtaining the category of

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axial symptoms. *Cognitive deficits* were assessed using the same four-point scale. Cognitive deficits refer to impairments in cognitive functions including thinking, memory and judgement, secondary to the development of the schizophrenic process. The number of hospitalisations and the total number of days spent in the hospital were assessed on quantitative scales considering only inpatient hospitalisations in general psychiatric wards. Not only the number and length of inpatient stays during the entire follow-up period (*number of hospitalisations 2*, *days in hospital 2*), but also data on the first five years after hospitalisation (*number of hospitalisations 1*, *days in hospital 1*) were included. The decision to additionally include a five-year follow-up period, inspired to some extent by the standards followed in oncology (where after five years without tumour recurrence it is possible to cautiously speak of a cure), referred to the solutions we adopted in the aforementioned longer follow-up (Ślosarczyk et al., 2022d), as well as to the even earlier follow-up studies on schizophrenia conducted in our centre more than 50 years ago (Bomba and Mamrot, 1981). The other ordinal variables were classified on a three-point scale (*regression*), a five-point scale (*relational abilities*, *education*, *working life*) or a six-point scale (*insight*) – with deep regression, ability to form mature bonds, higher education, very good professional functioning, and full insight as the top of the scales. Regression was understood as a return to earlier developmental patterns of psychological functioning, particularly in the area of defence mechanisms and relations with the object entailing confusion and helplessness. Insight was defined as referring to the awareness of mental illness. A dichotomous character was set to the variables including *gender*, *marriage*, *EEG pathology,* and *follow-up diagnosis of schizophrenia*, with female gender, the fact of a marriage, the fact of pathology in the EEG recording performed during the first hospitalisation and the follow-up diagnosis of schizophrenia as the top of the scales. The GAF is a 100-item ordinal scale that combines an assessment of the severity of psychopathology and the level of social functioning. The conditions of the present study were considered to allow assessment with a precision equivalent to five-point ranges. The *number of children* and *age of onset* were treated as quantitative variables. The symptoms of schizophrenia, cognitive deficits, insight, regression and relational abilities were assessed only by in-person surveys. For the remaining variables, other sources of information (questionnaires, documentary analysis, official data) were also used.

Statistical methods

When performing the statistical analysis of the data, we considered non-parametric tests (Mann–Whitney *U* test) to be more appropriate than parametric tests because of the lack of clarity about the normal distribution of the studied characteristics, a large number of outliers, and a considerable amount of dichotomous and ordinal data, which are not typically quantitative. $p < 0.05$ was considered as the statistical significance cut-off. The following statistical software was used for the analyses: IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp, Released 2012. Based on knowledge and clinical experience, it was hypothesised that the subjects in the schizophrenia group would, over time, exhibit lower levels of clinical and social functioning than the subjects in the acute and transient psychotic disorders group, meaning more schizophrenic symptoms, especially axial symptoms, more cognitive deficits, more frequent and longer hospitalisations, more frequent diagnosis of schizophrenia in the follow-up examination, deeper regression, lower relational abilities, poorer education and working life, poorer insight, less frequent marriage, fewer children, and lower GAF scores. Thus, one-sided significance was assumed to be meaningful in the analyses concerning the above parameters, and two-sided significance was used for the categories excluded from the initial hypothesis (*gender*, *age of onset*, *EEG pathology*). In view of the non-parametric nature of the statistical method used, the obtained significance measurements should be treated as asymptotic.

Limitations of the study

We are aware of the serious methodological limitations of our study. The design of the measurement scales used is marked by a certain arbitrariness. Undoubtedly, a weakness of the study is the fact that, except in particularly questionable cases, the results of the examination of individuals were not reconciled, and the researchers decided on the scores in different categories individually and independently. The number of study participants was low, and only half of the individuals could be examined in person. The fact that much of the data (on the course of treatment, education, work, personal life) could be obtained from other sources can only be a partial compensation, constrained by its own limitations. The limitations of the implemented statistical methods have already been discussed and justified in the previous section.

RESULTS

The first part of the results obtained in the between-group comparison is presented in Tab. 1.

The two study groups do not differ significantly in terms of *age of onset* and *gender*. The presence of *EEG pathology* in the recordings taken during the first hospitalisation is also not distinctive for any of the groups. The most significant differences concern the *sum of schizophrenia symptoms* and, in particular, its *axial symptoms* measured at time point 2. A significantly higher symptom severity was observed in the group with a baseline diagnosis of schizophrenia. This group was also distinguished by a significantly higher severity of *cognitive deficits* ($p = 0.001$). Differences in the *number of hospitalisations* and *days in hospital* appeared to be less pronounced, but both in the first five years after hospitalisation and in the entire 15 years afterwards, the subjects in the schizophrenia group had more frequent and

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	F20 group size	F23 group size	Arithmetic mean in group F20	Arithmetic mean in group F23	Mean rank in group F20	Mean rank in group F23	Mann–Whitney test value	Asymptotic significance (one-sided)
Gender	11	23			19.86	16.37	100.500	0.262*
Age of disease onset	11	23	16	16.3	16.68	17.89	117.500	0.738*
EEG pathology	10	21			17.65	15.21	88.500	0.308*
Sum of schizophrenia symptoms	7	10	6.86	0.2	13.14	6.10	6.000	**0.001**
Axial symptoms	7	10	4.71	0.2	13.14	6.10	6.000	**0.001**
Cognitive deficits	7	10	1.14	0.0	11.86	7.00	15.000	**0.0045**
Number of hospitalisations 1	11	23	2.45	1.09	22.09	15.30	76.000	**0.0245**
Days in hospital 1	11	23	85.9	34.9	21.77	15.46	79.500	**0.034**
Number of hospitalisations 2	11	23	4	3	20.73	15.96	91.000	0.0895
Days in hospital 2	11	23	184	96.7	21.36	15.65	84.000	0.0545

* Two-sided significance.
Bold indicates *p* values <0.05.

Tab. 1. Comparison of the groups with respect to selected indicators – part 1

aggregated longer stays in psychiatric hospitals. Differences assessed at the five-year sub-period level proved to be statistically significant. The second part of the comparison can be found in Tab. 2.

At time point 2, the group with a baseline diagnosis of schizophrenia presented features of deeper *regression* and a significantly weaker level of *insight*. These individuals had a significantly poorer working life and were significantly more likely to receive a *follow-up diagnosis of schizophrenia* than the respondents in the other group. The respondents in the schizophrenia group were also less *educated* at time point 2 and had lower *relational abilities*, which was presumably also linked to the observed less frequent *marriage* and lower *number of children*, and they scored lower on the GAF scale. However, the differences mentioned in the last sentence were not statistically significant, though it needs to be added that, with the exception of the *number of children*, the *p*-value obtained in their case was below 0.1.

DISCUSSION

In the contemporary literature, ATPDs appear as disorders characterised by low diagnostic stability over time, as compared to schizophrenia (Marneros et al., 2003). The diagnostic pathways of patients with ATPDs diverge over time in very different directions: from schizophrenia through schizoaffective and affective disorders to anxiety disorders and personality disorders and, not infrequently, to recovery. The low stability of diagnosis is even more pronounced in adolescent patient populations (Correll et al., 2008; Remberk et al., 2012). The results of our study are in line with these findings. A follow-up diagnosis of schizophrenia was made significantly less frequently in patients with ATPDs compared to baseline schizophrenic patients. Of the 19 patients with baseline ATPDs, in whom a current diagnosis could be established after 15 years, six were diagnosed with schizophrenia, five with affective disorder, two with schizoaffective disorder, one with anxiety disorder, one with personality disorder, one with alcohol dependence syndrome, and four were considered healthy. In the group of 11 patients with a baseline diagnosis of schizophrenia, who were successfully re-diagnosed after 15 years, nine maintained their diagnosis and the remaining two no longer met the criteria for any mental disorder. It is not surprising, though, that in this group of patients we found a significantly higher severity of schizophrenic psychopathology

	F20 group size	F23 group size	Arithmetic mean in group F20	Arithmetic mean in group F23	Mean rank in group F20	Mean rank in group F23	Mann–Whitney test value	Asymptotic significance (one-sided)
Regression	7	10	2	1.1	11.57	7.20	17.000	**0.0145**
Insight	7	10	4.28	5.5	5.43	11.50	10.000	**0.0035**
Relational abilities	7	10	2.86	4	6.86	10.50	20.000	0.0575
Education	11	18	2.82	3.28	12.36	16.61	70.000	0.0695
Working life	11	17	1.09	2.79	9.64	17.65	40.000	**0.0045**
Marriage	11	23	1.09	1.3	15.05	18.67	99.500	0.088
Number of children	10	17	0.3	0.59	12.60	14.82	71.000	0.2055
GAF	9	14	60.5	71	9.56	13.57	41.000	0.0805
Follow-up diagnosis of schizophrenia	11	19			20.27	12.74	52.000	**0.0049**

Bold indicates *p* values <0.05.

Tab. 2. Comparison of the groups with respect to selected indicators – part 2

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after 15 years, particularly in terms of the axial symptoms of schizophrenia, and a higher level of cognitive deficits. Interestingly, much smaller differences (also in favour of the ATPDs group) were found in the area of frequency and total length of re-hospitalisation. These were statistically significant at five years post-onset but lost significance after 15 years. These findings are essentially in line with the literature, with the authors noting that recurrence is a factor which shows relatively little difference between the two study groups (Marneros et al., 2003). On the other hand, it is worth noting that in our previous studies, the frequency and total length of hospitalisation in the first five years after the onset of the illness proved to be one of the more important remote negative predictors of the course of adolescent schizophrenia (Ślosarczyk et al., 2022d). Arguably, therefore, this factor also had its impact on the significantly deeper regression, lower levels of insight, and poorer quality of working life found after 15 years in schizophrenic subjects. In particular, the latter two indicators, i.e. the level of insight and occupational functioning, distinguished exceptionally sharply between the two study groups ($p < 0.005$) prejudging superior psychosocial adaptation in patients in the ATPD group. This result is consistent with predictions and it is confirmed by other follow-up studies, both those involving baseline adult patient populations (Marneros et al., 2003) and adolescents (Valevski et al., 2001). Thus, it appears that what determines the more favourable prognosis of ATPD compared to schizophrenia is not necessarily the lower relapse rate, but rather the different nature of the relapses themselves, entailing different consequences. This would confirm the view presented in the monograph by Marneros and Pillmann (2004) that different pathomechanisms underlie ATPDs and schizophrenia. This is also supported by current neurophysiological, neurometabolic, genetic, and immunological findings (Malhotra et al., 2019). All these considerations make it difficult for patients with ATPDs to fit into any pattern. They require a flexible and highly individualised approach to every patient, which represents a major challenge even for experienced clinicians. Their task involves identification of the above-mentioned hypothetical pathomechanisms and attempts to intervene in their area. The course of ATPDs can be highly variable and extremely difficult to predict (Damiani et al., 2021). It is no coincidence that such patients are often prescribed inadequate pharmacotherapy and, at the same time, are too rarely referred to psychotherapists for a precise analysis of the specific psychotic episode in terms of its psychogenesis (Minichino et al., 2019).

CONCLUSIONS

1. The respondents in the group with a baseline diagnosis of schizophrenia revealed a significantly higher severity of schizophrenia symptoms 15 years later, particularly the axial symptoms of the illness, as well as a higher severity of cognitive deficits. They were significantly more likely to receive a follow-up diagnosis of schizophrenia than the respondents with a baseline diagnosis of acute and transient psychotic disorders (ATPDs).
2. The patients with a baseline diagnosis of schizophrenia were more frequently and for a longer time hospitalised psychiatrically during the follow-up period, with the difference being more marked during the sub-period of the first five years after hospitalisation.
3. The people whose psychotic decompensation in adolescence was designated in the ICD-10 classification as F20, revealed a deeper regression, lower levels of insight, and poorer working lives 15 years later. The differences between the groups with respect to the latter two parameters reached a particularly high significance ($p < 0.005$).

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations that could negatively affect the content of this publication and claim authorship rights to this publication.

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