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Stages of the clinical course of schizophrenia – staging concept

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Summary

Clinical staging is a tool useful in medical sciences. It assumes the presence of three key elements. Firstly, pathologic indices are progressing in subsequent stages. Secondly, the patients in the individual stages present similar pathological changes. Thirdly, treatment should be most effective in the earlier stages. Such model is particularly well established in the treatment of malignancies. Staging is useful here to define prognosis, to evaluate the results of treatment, facilitate the exchange and comparison of information among treatment centres. There is much data describing a similar model for mental illnesses including schizophrenia. There are two theories supporting the staging model for schizophrenia: the neurodevelopmental hypothesis and allostatic load concept. Both theories make a theoretical premise for creating the staging model for schizophrenia. We can describe at least three stages in the development of a schizophrenic illness: the prodrome, the first episode and chronic phase. Each stage is reflected by anatomical and functional changes in the brain. Therefore, a clinical staging model can describe a development of schizophrenia over time, to help selecting adequate treatments that are particularly relevant to a given stage and to show the relations between known biological markers and psychosocial risk factors and the stage of the illness.

Key words: schizophrenia, staging, phases

Staging concept in medicine

In many fields of medicine, a description of the disease course in terms of separate stages, generally referred to as "staging", has been used for many years. It refers to the illnesses that had their particular stages described not only in the context of pathological and physiological changes but also therapeutic methods specific for a respective phase

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[1]. Therefore, the staging model assumes a developmental character of the illness in which three criteria should be met:

a) In subsequent phases the intensity of symptoms must be greater;
b) The progress to subsequent phase should be connected with a typical clinical picture;
c) The treatment in initial phases of the illness is more efficacious [2].

The concept of staging assumes the use of this model for diagnostic and cognitive purposes, therefore, the construction of particular phases has to be based on precisely documented anatomical, physiological, biochemical and clinical factors. Based on this model, the proposed therapy can be implemented earlier; it will be safer, more effective and resulting from a well-defined biological basis. Also, the assessment of the effectiveness of treatment will be more precise, both in the clinical context and economic burden [3].

In its most classical conceptualization, staging refers to cancer. Albert Broders, an American pathologist, was the forerunner of research in this field. In 1920 he proposed to number cancer stages with an independent prognostic marking for each phase. This system has been widely accepted [4] and has developed into presently used classification TNM (tumor node metastasis) where T describes the size of the primary tumor, N stands for regional lymph nodes that are involved, and M describes the presence or lack of distant metastases [1]. This system allows for the use of the standardized diagnostic and therapeutic methods, the standardized evaluation of the effects of treatment and the exchange of information between different centers. Another example of using staging for comprehensive evaluation and treatment is coronary artery disease. Implementing staging procedures allows for an individual risk assessment of the development of the disease (genetic factors, lifestyle), its progress (e.g., high blood pressure, metabolic syndrome) and the severity of clinical signs (e.g., angina pectoris) [5]. As a result, the applied treatment can be adjusted to the individual needs of the patient and to the phase of the illness, beginning with the preventive actions (diet, exercises), through pharmacological, up to surgical methods (stents, coronary artery bypass grafts etc.) [5]. Diagnostic and therapeutic effectiveness of the staging, along with a possibility to exchange information and experience between different treatment centers, has resulted in popularization of this method in many diverse fields of medicine, such as treating obesity [6], amyotrophic lateral sclerosis [7] or Chagas disease (American trypanosomasis) [8].

Staging in psychiatric disorders

Clinical usefulness of staging encouraged the representatives of other fields of medicine, including psychiatrists, to implement that model in their specialties. In psychiatry, establishing strict diagnostic criteria for respective phases of the illness, in

accordance with staging, would allow to differentiate early symptoms of the illness from developmental variants or normal behaviors characteristic for a particular stage of life [9]. Contemporary classifications, mainly in the areas of psychotic and mood disorders, dating back for 100 years, are characterized by low diagnostic value before full development of the illness. Lack of strict diagnostic criteria for the early phase of the illness leads to the use of drugs or the extension of the indications for their use without the explicit clinical evidence [9]. It leads to activities incompatible with the guidelines of many expert groups elaborating standards for the treatment of schizophrenia, which recommend the introduction of possible careful neuroleptic therapy only when specific criteria of disease are fulfilled [10]. Implementation of staging in psychiatry will allow leaving out determinism, replaced by a modern approach taking into account genetic and environmental factors and their influence on the beginning and course of the illness. It is important to note that mental disorders are becoming more common and that most of the recognized mental illnesses occurs in people at the age of 25 or less, often progressing from early developmental disorders to a full psychiatric syndrome [11]. In 1993, Fava and Kellner [12] proposed how to use the staging model in psychiatry, pointing to its usefulness in describing schizophrenia, recurrent depression and anxiety disorder. In recent years, many well-documented models of staging for bipolar affective disorder and unipolar disorder have been proposed. In Poland these topic have been covered in papers by Ferensztajn and Rybakowski [13] and Ferensztajn et al. [14]. Also, the attempts have been made to describe schizophrenia according to the rules of staging.

Schizophrenia as a neurodevelopmental disorder

In order to create a similar model for schizophrenia, it was necessary to distinguish certain stages that would reflect anatomical and physiological changes in the brain, along with characteristic accompanying clinical symptoms [1]. In this context, the model of staging is complementary with the neurodevelopmental concept of schizophrenia. According to this concept, etiological and pathological factors of the illness appear much earlier than its clinical manifestation [15]. Genetic determinants and environmental factors occurring already in the fetal life, most often at the end of first and beginning of the second trimester of pregnancy, lead to changes in the development and functioning of the brain in adolescence and adulthood [16]. Normal development of the central nervous system may be disturbed by many environmental factors such as perinatal hypoxia, intraventricular hemorrhage [16], diabetes, hemorrhage during pregnancy, serological conflict, low birth weight, pre-term birth [17] and viral infections [18]. Hare et al. [19] and Machon et al. [20] described higher frequency of schizophrenia among children born in late winter and early spring as a result of influenza virus infection of their mothers. At present, besides of influenza virus, a pathogenic role of the rubella virus, the herpes group viruses and cytomegaloviruses [16], retroviruses [18],

as well as e.g., Toxoplasma gondii [21] has been also considered. Viruses influence the fetus directly [22], through activating cytokines, mainly the pro-inflammatory ones (e.g., IL-1, IL-2, TNF-alpha) in mothers or fetuses [23] as well as through influencing gene expression in the brain of the developing fetus [16]. A number of other environmental factors that can influence the development of the central nervous system has been also postulated. One of them is head trauma in childhood. Abnormalities in the development of brain can also have secondary character resulting from genetically determined cognitive dysfunctions among those at risk of developing schizophrenia [17]. Treating cognitive disorders as primary in schizophrenia is a classical Kraepelin's concept focusing on the core disorder of those functions in schizophrenia patients. According to Kahn, an impairment of cognitive functions and intelligence predate by several years the occurrence of psychosis among patients with schizophrenia [24]. Another environmental mechanism that, according to some research, increases the risk of schizophrenia by four-fold is using cannabinoids in adolescence [17]. Other environmental factors are migration [25] and urbanization [26]. Their influence on central nervous system still needs further research, though one may presume that toxic factors (pollution of the environment), diet, infections and stress play a significant role [17] in pathogenesis of schizophrenia.

Neurobiological evidence for the concept of staging in the light of neurodevelopmental theory of schizophrenia

The first neuroimaging studies of the central nervous system structures in schizophrenia showed a widening of the lateral ventricles, third ventricle and the pits and fissures of the brain. The study conducted by Johnstone et al. [16] found cortical atrophy, reduced volume of the amygdala, thalamus and hippocampus. Results obtained in later neuroimaging and functional studies confirmed the presence of significant differences in the structure and function of the brain between patients with schizophrenia and the control group. Researchers from the McGorry's group observed, among others, the reduction of the volume of gray matter in the frontal cortex in the early phase of the illness, with a tendency to intensification of those changes in later periods. There was no enlargement of the lateral ventricles in the initial phase, it appeared in later stages, and similar results were obtained for hippocampus, superior temporal gyrus and insular cortex [2]. These changes intensified significantly in the late stages of the illness. Similar results were obtained by assessing the volume of white matter. Differences between the control group and patients with schizophrenia appeared already at the beginning of the illness, and related mainly to the right superior temporal lobe and corpus callosum (frontal gyrus). The changes progressed in the course of the illness, regarding e.g., corpus callosum, in the late phase concerned anterior genu, posterior genu and isthmus [2]. Studies using functional magnetic resonance showed a decrease in the activity of

several cortical regions (mostly in the prefrontal cortex) between the control group and patients with schizophrenia, proportionally to the respective phases of the illness [2]. However, it should be noted that in some papers the authors did not observe any major changes in the structure of the brain or they were difficult to classify [27, 28].

Studies using MR-SMR spectroscopy have shown the presence of differences in the concentration of N-acetylaspartate (NAA) and various phosphomonoesters in prefrontal and temporal cortex. Concentration of these substances may reflect neuronal and glial mass. The NAA concentrations in the temporal region are reduced already during the first episode. Studies of patients in the first episode of schizophrenia show a decrease in the concentration of phosphomonoesters in the prefrontal cortex suggesting an increase of phospholipid metabolism. This is probably a result of disturbances in cell membranes in response to the pathological process, such as a significant reduction of synaptic connections. In a study of patients in various stages of the illness, a higher concentration of glutamine in schizophrenia than in the control group was observed. This correlated positively with the duration of the illness [13].

Besides of abnormalities in neuro – and functional imaging of the brain in schizophrenia patients, also the so-called neurological soft signs (NSS) may appear, distinguishing healthy subjects from the patients and the patients in various phases of the schizophrenic process [29]. The NSS mean slight, objectively measurable neurological abnormalities of specific location in the brain, reflecting abnormal subcortico-cortical or cortico-cortical connections [26]. The most noticeable NSS include, among others, mutual suppression, visual-auditory integration, errors in the finger-to-nose test, and reflexes (glabellar reflex, jaw jerk reflex, snout reflex and others). Since the NSS are associated with the enlargement of the brain ventricles and reduction of some of its areas, their presence and intensity may correlate with different phases of schizophrenia, in accordance with the theory of neurodevelopment and staging [29].

The concept of allostasis can be supplementary to the neurodevelopmental theory of schizophrenia. This concept explains the cascade of pathophysiological processes leading to the development of the illness, especially in terms of progressive development of dysfunctions and various stages of this process. The concept of allostasis assumes maintenance of the consistency of internal environment by changing the functioning of particular body systems, so-called allostasis mediators. In response to prolonged activity of pathogenic agents, the accumulation of allostasis effects results in the development of adverse multiple changes in the body, the so-called allostatic load (AL) [30]. Allostasis mediators include hormones, neurotransmitters, neurotrophins, mediators of oxidative stress, and indicators of inflammatory processes [31]. The factors triggering allostatic cascade include changes in the structure and function of neurons in schizophrenia, such as metabolic disturbances of membrane phospholipids [32], dysfunction of receptors for mediators of the immune system [33], changes in the axonal and dendritic structure and function of neurons [34]. In this perspec-

tive, the theory of allostasis fits and complements the concept of staging. Allostatic load proceeds in several stages. In response to stress factors, the so-called primary mediators (glucocorticoids and catecholamines) are activated. They cause a series of processes at the cellular level (an inflammatory response, oxidative stress, activation of neurotrophins and cytokines). In the next step, the effects at the level of tissues and organs (body weight change, blood pressure fluctuations, changes in the level of cholesterol, glycosylated hemoglobin, C-reactive protein, insulin, fibrinogen, etc.) can be noticed. The final step and at the same time the effect of the allostatic load, is an illness/syndrome (e.g., schizophrenia) [31].

According to the neurodevelopmental theory, factors disrupting brain development increase susceptibility to the development of psychosis. In the premorbid phase, stress-induced allostatic load along with the biological predisposition becomes a factor triggering the onset of psychosis. In addition, the phenomenon of allostatic load occurring in the course of clinically overt psychosis worsens its course and prognosis leading also to the coexistence of mental and somatic disorders and to the progress of changes in the central nervous system [31].

Concepts of staging in schizophrenia

Studies on the course of schizophrenia including the premorbid and prodrome stage as well as the need for a quick and adequate reaction already at that stage have a relatively short history. In the PubMed database the first article entitled “Early intervention in schizophrenia” was entered in 1993 [35]. It was not until the development of modern neuroimaging, functional and genetic studies that a broader, not only clinical, perspective of schizophrenia as a neurodevelopmental illness with all its consequences was allowed.

In the classical term, schizophrenia is an illness that runs in three stages, among which we distinguish the prodromal phase, the first episode and the chronic phase [36]. Neuroimaging and neuropsychological studies evaluating cognitive function indicate the presence of the pre-prodromal phase with often minimal abnormalities in the central nervous system and in social and emotional development [37]. The study of Pantelis et al. [38] is considered to be pivotal in the field of neuroimaging. Using magnetic resonance, they described neuroanatomical changes in the brain structure of patients with schizophrenia in different phases of the illness. They observed, among other things, the grey matter loss in the temporal and frontal area, characteristic for the prodromal phase [38]. Marshall et al. [39] noticed that those changes appear rapidly in the first months and even in the first weeks of psychosis. Studies on the brain activity with the use of functional magnetic resonance were performed by Broome et al. [40]. They analyzed a group with high risk of developing psychosis, a group with the first episode of the illness and a control group. People from the high risk group were characterized by worse activity of the left inferior parietal cortex when

compared with the control group, although better, when compared to the group with an overt clinical psychosis. This shows the gradual change in the brain of people predestined to develop psychosis. Authors of these studies, in line with the concept of staging, introduced a term "ultra high risk group" (UHR). This group includes people with a family history of psychosis, subclinical psychotic symptoms as well as deficits in functioning. A more precise definition of the UHR was given by Young et al. [41]. This definition includes people aged 14–29 years who had at least one of the following symptoms:

a) transient psychotic symptoms within the last 12 months;
b) short-term acute psychotic episode lasting no longer than 7 days, with spontaneous remission;
c) schizotypal personality traits;
d) deteriorating social, family or professional functioning in the past year.

The validity of identifying such a group was confirmed by studies which showed that 40% of these persons develop full-blown psychosis within the 12-month period. Summarizing the processes occurring in the brains of people with a predisposition to schizophrenic psychosis (UHR), Moller [42] distinguished three phases: neurodevelopmental process in the premorbid phase associated with genetic and environmental factors; a period of intense changes in the early adulthood related to the processes of apoptosis and remodeling of adult brain; and the phase of changes occurring along with the first psychotic episode.

While discussing suggested changes in the structure and function of the brain in different stages of development of schizophrenia it should be noted that some of these changes result not from the illness process but it may be determined by such factors as stress, psychoactive substances, poor diet, smoking, social and economic influences and medications other than antipsychotics [38].

Based on theoretical grounds of staging, many researchers proposed their own concepts of describing schizophrenia. It seems that those using objective research data in accordance with clinimetrics (field of medical science which deals with the development and use of methods allowing to measure clinical phenomena occurring in a patient) should be regarded as the most significant [12, 43]. The first description of staging in psychiatry that used clinimetric methods dates back to 1993. Fava and Kellner [44] proposed 5 stages that described the development and course of schizophrenia:

- Stage 1 – prodromal phase treated as affective disorders and negative symptoms with impaired functioning;
- Stage 2 – acute psychotic episode;
- Stage 3 – residual phase;
- Stage 4 – prechronic (between the 6^{th} and 24^{th} month of the illness duration);
- Stage 5 – chronic (duration of the illness > 24 months).

Table 1. **Stages of the course of schizophrenia according to McGorry et al. [9]**

Stage	0	1a	1b	2	3a	3b	3c	4
Symptoms	No symptoms. Risk of psychotic disorder	Mild or nonspecific symptoms, mild neurocognitive deficits, mood disorder	Moderate or subthreshold symptoms, moderate neurocognitive changes, GAF 70	First psychotic episode or severe mood disorder (mania or persistent depression), GAF 30-50	Incomplete remission from first episode	Recurrence of psychotic or mood disorder, residual symptoms, proceeding neurocognitive deficits	Multiple relapses	Persistent or unremitting illness, disability criteria
Markers	Smooth pursuit eye movements, niacin sensitivity, olfactory deficits, HPA dysregulation markers, binocular rivalry, prepulse inhibition, mismatch negativity, P50	As in 0	Niacin sensitivity, folate status, oxidative stress markers, HPA dysregulation markers, MRI and MRS changes	As in 1b	As in 1b	As in 1b	As in 1b	As 1b
Interventions	Psychoeducation training, cognitive and social skills training	Family psychoeducation, counseling, substance abuse reduction	Family psychoeducation, cognitive-behavioral therapy, substance abuse reduction, neuroprotective agents (for example, omega-3)	Family psychoeducation, substance abuse reduction, atypical antipsychotic agents, antidepressant agents or mood stabilizers, rehabilitation	As for 2 with additional pharmacological and psychosocial strategies	As for 3a with emphasis on relapse prevention	As for 3b with emphasis on long-term stabilization	As for 3c with clozapine and social support

Agius [1] proposed a four-phase model: a period of high risk of development; first episode; critical period and chronic phase. McFarlane [45] put it in a more elaborate form:

- Phase 1 – premorbid state, slight indicators of disturbance of thinking and functioning;
- Phase 2 – prodrome stage, slight psychotic symptoms, not meeting the criteria for diagnosing schizophrenia;
- Phase 3 – the first full-blown psychotic episode, 75% chance of recurrence, 25% chance of complete remission;
- Phase 4 – chronic illness, numerous relapses, significant disruption of functioning.

The most developed model of schizophrenia based on the principles of staging was proposed by McGorry et al. In this model, the authors identified 8 stages of the illness development. For each stage, they defined clinical picture, a type of intervention and specific biological markers. Table 1 summarizes the main features of the concept of staging in schizophrenia by McGorry [9].

McGorry's model is characterized by the most comprehensive and complete approach, both diagnostically and therapeutically. The qualification to various phases is based on the clinical picture of the illness as well as biological markers. So-called endophenotypes are behavioral and neurophysiological indicators suggesting the risk of developing schizophrenia [46]. According to the recent studies, their diagnostic role is becoming more important as 73% of psychosis is preceded by a period of one to two years of nonspecific symptoms; only 18% begins in an acute manner and with prodromes lasting about four weeks [40]. Additionally, McGorry points to the social context of developing the illness, among other things, identifying sources of information about the patient. Most importantly, he points to certain patterns of conduct adequate to the phase and the severity of the illness, all in accordance with the principle of staging.

Therapeutic implications of staging in schizophrenia

The idea of staging aims to improve the efficiency of diagnosis of schizophrenia as well as development and unification of therapeutic strategies. Based on the McGorry model, the following steps of therapy are proposed.

In stage 1 (prodromal phase), the aim is to prevent the development of full-blown psychosis [1], and to inhibit apoptosis processes and the damage associated with the oxidative stress. It is recommended to use family therapy, cognitive-behavioral therapy, neuroprotective agents (for example, omega-3) and prevention of addictions [9]. In stage 2 (first episode of psychosis and first three years of the illness), the aim is to reduce the acute symptoms of the illness, inhibit cognitive deficits and to make a return to family life and professional life. Along with the neuroleptic treatment, it is recommended to monitor cognitive functions, to treat post-psychotic depression,

to employ family and cognitive therapy as well as psychoeducation. The ultimate goal of therapy is to achieve complete remission of symptoms and to prevent relapse of psychosis [47]. In stage 3 (chronic psychosis), the therapy should prevent further exacerbation of the illness, by the use of clozapine, long-acting drugs and new antipsychotics, along with psychoeducation and social therapy in order to maintain social functioning, family and professional life [1].

Particularly noteworthy are proposals of intervention in the early stages of the illness. Studies show that actions undertaken already in the prodromal phase, even if they do not inhibit the development of psychotic symptoms, significantly improve later functioning of the patient [48]. A study in which a group of UHR patients was provided with an early pharmaco-and psychotherapeutic intervention showed reduced incidence of the development of psychosis (9.7%) compared to 35% in the control group [49]. Interesting results were also obtained in a study that compared the incidence of development of full-blown psychosis in the UHR group divided into a behavioral-cognitive therapy subgroup and a control subgroup (6% vs. 26%) [50]. Essential fatty acids (EFAs) are thought to be a potential early pharmacotherapy. In a study published in 2010, a group of patients fulfilling the criteria of phase Ib, according to McGorry, has been divided into a subgroup receiving EFAs and a subgroup receiving placebo. During the 52 weeks of the study, 27.5% of patients from the placebo group developed phase II compared with 5% of the group receiving essential fatty acids [51]. Those methods seem to be effective only with respect to phase Ib, and their therapeutic efficacy in phase II and further, is much smaller [2].

Promising results of the above-mentioned observations lead to a proposal to create a strategy of the so-called indicated prevention aimed at early detection and rapid elimination of the so-called warning signs among people at risk of psychosis [52].

Recapitulation

Application of staging method in psychiatry raises hope for improvement of care and better results of treatment in people suffering from severe mental illnesses. Nevertheless, some doubts that are associated with this diagnostic and therapeutic approach should not be ignored. A certain limitation of staging is the fact that the assessment of many symptoms is retrospective, and some symptoms, such as mood disorders, concentration difficulties, sleep disorders, neurotic symptoms, may be not specific. Likewise, the assessment of treatment effectiveness may raise controversies. Observed symptoms may have residual character but may also develop from premorbid personality traits. Apart from the effect of the patient's personality on shaping the symptoms and on the course of disease, also psychological factors (e.g., psychological trauma) and socio-economic factors (e.g., community support) are more important in mental illness than in somatic diseases for which the staging model has been functioning for many years [53].

There are also ethical and moral dilemmas associated with the unquestionable stigmatization and the scope of informing the patient about a hypothetical possibility of developing mental illness. It seems necessary to obtain patient's consent in order to initiate therapeutic procedures before clinical manifestation of the illness and to secure a close cooperation in order to evaluate potential positive results and possible side effects or adverse events.

These doubts lead some authors [53] to the proposals of creating individual classification based on the methods of staging for each patient, taking into account the individual course of disorder and full psychosocial context.

Regardless of these doubts and possibility of practical application of staging in psychiatry, it is a method which, by referring to a holistic view of the patient and his suffering, gives hope for better utilizations of diagnostic and therapeutic methods owned by modern psychiatry.

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