4. General overview

4.1. Definition

Schizophrenia is a severe psychotic mental disorder characterized by significant disturbances of mental functioning. It has also been called “early dementia”, “intrapsychic discordance” or “autistic dissociation of personality”.

Historically, at the end of the 19th century, the different clinical manifestations of schizophrenia were called “dementia praecox” by Morel, in France, “hebephrenia” (demential state in young people) by Hecker, in Germany, and “catatonia”, referring to psychomotor disorders, by Kalhbaum. Kraepelin combined all these types into one nosological entity that he defined as “early dementia”. He distinguished three clinical forms: simple or hebephrenic, catatonic or paranoid, the latter characterized by delusions.

Many authors from that time period already recognized that it had less to do with dementia than it did with dissociation of psychic life, which loses its cohesiveness. It is this notion that is reflected in the concept of “schizophrenia” developed by Bleuler in 1911. This process is characterized by a deficitary syndrome of dissociation and by a secondary syndrome of generation of ideas, feelings and delusional activity. The current definition was developed based on this conceptualization.

The term schizophrenia refers to a series of psychotic disorders, characterized by the presence of positive psychotic symptoms at some point of their evolution, and where negative and cognitive symptoms are associated with a variable degree of disability. Their basic manifestations consist of a mixture of characteristic signs and symptoms. Symptoms affect multiple psychological processes, such as perception (hallucinations), ideation, loss of connection with reality (delusions), thought processes (loose associations), feelings (flat affect, inappropriate affect), behaviour (catatonia, disorganization), cognition (attention, concentration), motivation and judgement. There is no symptom that, by itself, is pathognomonic of schizophrenia. These psychological and behavioural characteristics are associated with several types of impairment. The characteristic symptoms of schizophrenia have often been classified into two big categories –positive and negative symptoms (or deficits)-, to which a third category has been recently added, disorganization. Not all symptoms described are present in every patient diagnosed with schizophrenia. They are not specific, given that they also occur in other diseases. The disorder is characterized by great heterogeneity amongst different individuals and variability in each of them over time. It is also associated with increased incidence of general medical diseases and mortality, especially by suicide, which occurs in up to 10% of patients.
4.2. Natural history and course

The onset of schizophrenia can occur during adolescence—even during childhood— or in adulthood. It affects both sexes in a similar way. However, in males, the most frequent age of onset is at the beginning of the third decade of life, whereas in women, it is at the end of the second decade of life or beginning of the third. Generally, women are more prone to present late onset schizophrenia. Onset may be acute or insidious. In the clinical course of most patients acute psychotic episodes alternate with stable phases of total or partial remission. This disorder, which is often chronic, can be characterized by three phases which overlap with no clear or absolute limits between them. These phases comprise the structure to integrate the therapeutic approaches described in this CPG.

- **Acute phase (or crisis).** During this phase, patients present severe psychotic symptoms, such as delusions and/or hallucinations, and severely disordered thinking; and, overall, are not able to properly take care of themselves. Often, negative symptoms also become more intense.

- **Stabilization phase (or postcrisis).** During this phase, the intensity of acute psychotic symptoms decreases. This phase can last six or more months after the onset of an acute episode (or crisis).

- **Stable phase (or maintenance phase).** Symptomatology may have disappeared or be relatively stable and, if persistent, is almost always less severe than in the acute phase. Some patients may be asymptomatic; others may present non-psychotic symptoms, such as tension, depression or insomnia. When negative (deficits) and/or positive (delusions, hallucinations or thought disorders) symptoms persist, they are often present in non-psychotic attenuated forms (for example, illusions instead of hallucinations or overestimated ideas rather than delusions).

Prior to the relapse of a patient who is in the stable phase, there is usually a prodromal period in which there may be non-psychotic dysphoric symptoms, attenuated forms of positive symptoms or idiosyncratic behaviours. The prodromal period may last between several days and several weeks, but may sometimes last for several months. Most longitudinal studies on schizophrenia suggest that its course is variable; in some patients there are no new episodes, in most of them there are exacerbations and remissions, and a small portion of them present a severe chronic psychotic state. Given the differences that exist in diagnostic criteria used in the studies that have been conducted, it is not possible to elaborate an exact and complete summary of the long-term evolution of schizophrenia.

Complete remission (restoration of the function that existed prior to the onset of the disorder) is not frequent in this disease. Of the patients who continue to suffer the disease, some seem to maintain a relatively stable course, whereas others present progressive worsening associated with severe disability. In the initial phase of the disease, there may be increasing negative symptoms that manifest mainly as prodromal disturbances. Subsequently, positive symptoms appear. Given that positive symptoms respond especially well to treatment, it is common for these symptoms to decrease with treatment; however, negative symptoms may persist. It has
been suggested that negative symptoms may intensify in some patients over the course of the disease.

The course of the disease may vary depending on whether treatment is instaured in early stages and on the health care response that the patient with schizophrenia obtains early on in the course of disease. Additionally, in relation to treatment, the evolution of scientific progress (development of new drugs, genetic studies, design of new psychosocial approaches, new treatment areas, etc.) gives hope to the future of treatment of patients with schizophrenia and their families.

During the 1990s interest in the first episodes of mental disorders grew, which led to placing greater attention on the initial phases of established severe mental disorders. In the field of psychotic disorders, interest focused on disorders such as schizophrenia, bipolar disorder, and others shifted to increased interest in the first episodes of psychosis. This interest was based on the hypothesis that an initial treatment of more severe mental disorders would improve their clinical course, and, therefore, their prognosis. This idea was strengthened by the knowledge that very long periods of time would elapse between the onset of a psychotic disorder and its acknowledgement and therapeutic intervention, which would be called duration of untreated psychosis. The reduction of this period would entail the possibility of secondary prevention.

This position gradually gave way to an interest focused on the prodromal manifestations of psychotic disorders, resulting in different conceptualizations and operative definitions of these manifestations, such as prepsychosis, preschizophrenia, hypopsychosis, prodromal symptoms or mental states at risk. The recognition of populations with these clinical characteristics could facilitate early intervention. The initial methodology followed to identify the psychopathological characteristics of psychotic disorder prodromes was the retrospective study of preceding symptoms and signs. In the 90s, Häfner and collaborators developed a standardized instrument, the “Interview for the Retrospective Assessment of the Onset of Schizophrenia” (IRAOS). Likewise, other authors used retrospective descriptions to characterize psychotic prodromes, based on basic symptoms, or other similar methodologies.

Another research line focused on the clinical manifestations which preceded a relapse (relapse prodromes) in patients diagnosed with schizophrenia. Yung and McGorry, based on the previous retrospective and relapse prospective studies, developed the theory that the manifestations of psychotic prodromes could be divided into eight subtypes: 1. Neurotic symptoms; 2. Mood-related symptoms; 3. Volition changes; 4. Cognitive changes; 5. Physical symptoms; 6. other symptoms; 7. Behavioural changes and 8. Attenuated (subthreshold) or isolated psychotic symptoms. The most frequently reported prodromal symptoms in retrospective studies were: reduced concentration and attention, reduced impulse and motivation, depression, sleep disorders, anxiety, social isolation, distrust/suspicion, functional deterioration and irritability. The category of attenuated (subthreshold) or isolated psychotic symptoms corresponds to experiences that are similar to psychotic features, but differ from true psychotic symptoms in terms of intensity, frequency and/or duration. As can be easily assumed, not all symptoms will be present in all patients or continuously in the same individual, and there is wide variability in how they present.
More recent works have focused on the prospective identification of prodromes, once their clinical characteristics have been identified, to enable both research and intervention. However, it must be taken into account that prodromal manifestations are not specific, and can be caused by different clinical conditions, such as major depression, substance abuse, somatic diseases, or a psychotic disorder. Amongst non-specific prodromes, the following should be highlighted: changes in the sense of “I”, feelings of tiredness, lethargy, lack of motivation, depression, anxiety, preferred isolation, eccentricity and difficulty studying or at work. More specific prodromal manifestations include: unusual ideas or beliefs, distrust/suspicion, grandiosity, sensation that the appearance of things has changed and difficulty thinking clearly. In young people the first symptoms are social withdrawal, anxiety and worry. Also, attenuated or isolated psychotic manifestations are not necessarily deterministic of a true psychotic disorder.

The concepts of at risk mental states (ARMS) and high and ultra high risk mental states (HRMS/UHR) have been introduced to describe these populations. High risk populations are characterized by the presence of initial psychotic symptoms. Furthermore, three high risk subtypes have been established: 1. Presence of attenuated (subthreshold) psychotic symptoms; 2. History of brief and limited psychotic symptoms, and 3. Positive family history of psychosis and persistent low functional level. These criteria have been tested in different studies to confirm their validity and to assess in a detailed manner threshold and subthreshold psychotic phenomena, as well as other signs and symptoms that appear in psychotic prodromes, including negative, dissociative and so-called “basic” symptoms.

Hence, when considering the natural history and course of schizophrenia, one cannot ignore all the research conducted in the past few decades which establishes a sequence from the prodromal phase until the establishment of schizophrenia and posterior evolution. In this sequence two big moments are considered: the first, which includes the early phases of psychosis, and the second, which encompasses the different phases of schizophrenia. This classification enables the subdivision of these moments into the following phases:

a. **Early phases of psychosis**, which include the high risk mental state or prodromal phase, the first psychotic episode phase and the recovery phase and critical period.

b. **Phases of schizophrenia**, which include the acute phase, the stabilization phase and the stable phase.

### 4.3. Epidemiology

The prevalence of schizophrenia over the course of a lifetime is variable, but results from the majority of studies establish an overall mean rate of less than 1 case per 100 inhabitants. The disorder seems to be uniformly distributed throughout the world, even though there may still be some pockets with high or low prevalence.

In regards to incidence, the *First episodes of schizophrenia in Cantabria* study reported that the incidence of schizophrenia in the 15-54 years risk age was 1.9/10,000 inhabitants per year, and that there were no statistically significant differences between sexes. Mean age of disease onset is 26 years, and it is significantly higher in women than in men.
Given that the onset of schizophrenia usually occurs in early stages of life and is often chronic, the costs derived from this disorder are considerable. In the United States, according to the review of studies conducted by the American Psychiatric Association (APA) schizophrenia accounted for 2.5% of the total direct costs of health care; that is, 16,000-19,000 million dollars in 1990. Indirect costs derived from factors such as the loss of productivity and the burden on the family were estimated to be approximately 46,000 million dollars. Furthermore, unemployment rates can reach 70-80% in severe cases and it is calculated that schizophrenic patients constitute 10% of the population in permanent disability.47

A review of studies examined data regarding the frequency of this disorder. The incidence of schizophrenia, its prevalence and the first psychotic episodes are successively described below.57

**A. Incidence of schizophrenia.** The international multicenter study performed by the World Health Organization (WHO) to determine the ratios of incidence in eight locations of seven countries and the publication of the preliminary report showed that the incidence of schizophrenia ranged from 7 to 14 for every 100,000 inhabitants per year. The authors concluded that the results supported the notion that schizophrenia occurs with comparable frequency in different populations.58, 59

However, a review of 158 studies performed between 1965 and 2001 in 32 different countries enabled the establishment of a mean annual incidence of 15.2 per 100,000 inhabitants per year, with higher rates ranging from 7.7 to 43.0 per 100,000 inhabitants per year in developed countries. Two independent systematic reviews showed differences in incidence depending on the patient’s sex, with significantly higher rates for males (male-female ratio 1.42/1.00). There were also higher incidences in urban areas versus rural areas, migratory status and birth month, with higher incidences in winter months.60-62

Later studies demonstrated heterogeneity in the causes of incidence of schizophrenia and other psychotic syndromes based on the AESOP study performed in three centres in the United Kingdom with a population of 1,600,000 inhabitants. Schizophrenia presented higher incidence in males (2.3/1.0); psychotic disorders were more frequent in black and minority ethnic groups, and differences related to age and geographical area were also reported. The authors conclude that there are independent and significant variations in schizophrenia and other psychoses in terms of gender, age, ethnic group and geographical area.63

**B. Prevalence of schizophrenia.** A SRSE of 188 studies published between 1965 and 2002 on the prevalence of schizophrenia in 46 countries reported that prevalence ranges from 4 to 7/1,000, depending on the type of estimation employed, although there were substantial differences between different geographical areas. The same review found raised prevalence in migrant populations.64

**C. Frequency of first psychotic episodes.** A study performed in rural Ireland on first psychotic episodes between 1995 and 2003, focused on the incidence of schizophrenia, bipolar disorder, mania and major depressive disorder with psychotic episodes, yielded an annual incidence of all forms of psychosis of 31.6/100,000 inhabitants per year, with higher values in males. For schizophrenia, incidence was 7.0; for schizoaffective disorders, 2.0; and for
schizophreniform disorder, 1.8. Affective psychoses presented an incidence of 11.6/100,000 inhabitants per year, and for brief psychotic disorder, delusional disorder and other psychotic disorders, incidence was 9.3/100,000 inhabitants per year. These data contrast with the results obtained in the study performed in Cantabria that was described at the beginning of this chapter.56

Lastly, mortality in schizophrenia should be considered from an epidemiological perspective, given that mortality in schizophrenic patients is consistently and significantly higher, in a two to three fold higher proportion, than that of the general population. The causes of this raised mortality should be sought in different factors such as suicides and violent deaths, non-cardiac natural deaths, cardiovascular diseases and use of antipsychotics and polypharmacy.66