Editoriale

At-risk mental states: possible clinical and theoretical developments

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At-risk mental state (ARMS) is a clinical condition characterized by a possibile development towards a psychotic disorder; early detection of ARMS is currently a focus of the scientific community.

From an etiopathogenetic perspective, the construct of ARMS is happily married with the neurodevelopmental model, in which the onset of psychosis is a long-term process that starts with a risk load that is based on genetic factors. Toxic, infectious, and metabolic factors are putatively involved during pregnancy; perinatal complications and early relational experiences are involved in this process from birth onward.

Neurodevelopment is a delicate process of sequential, timely changes leading to growth and the assumption of something appearing as a definite form, which regards both brain and other nervous structures and functions as well. Of course, the brain continues to develop throughout life by means of plasticity, much as a person, who is not exactly the same of the day before, but who appears to be so as an adult. Suffices it to skip some months or year of observation, and the person will appear different to the observer. The brain works much like this; when one is a kid, he may change rapidly, and changes are likely to be grossly observable, day by day. It is this period of growth in which dynamic interplay between pathogenic and protective factors occurs, increasing or decreasing the risk for psychosis, respectively. This dynamic interaction between proneness and resilience may result in epigenetic changes that constrain further individual trajectories. Moreover it may ensue in unpredictable processuality, whose variability is shown by wide phenotypic differences in transverse and longitudinal cuts of psychotic illness.

On the basis of the neurodevelopmental theory (1-3), there is a defect in brain circuitry connectivity (4). In particular, corticolimbic circuitries are "miswired", i.e., neurons are connected with the "wrong" neurones (5,6), leading to a sort of "cognitive dysmetria" (7).

Neurofunctionally, there results an attention deficit, impaired working memory and other executive functions, and dysfunctional emotional regulation.

Neuropsychological abnormalities and soft neurological signs, no matter how nonspecific they might be, may help detecting risk of psychosis prior to the full-blown onset of illness.

From a clinical perspective, the prodrome is a symptomatological forerunner of a disorder or a disease and is expected to invariably give way to the pathological process. The conceptualization of ARMS derives from an epistemological and nosological reversal of the prodrome (8), that loses its retrospective connotation to become a phase of the disease, viewed in a perspective.

These two links, one with the etiopathogenesis of the disease and one with its nosodromy, are postulates of the concept of "risk", as it is conceived in the contexts of early detection and early intervention.

The ARMS criteria, called also Ultra High Risk (UHR) criteria, were developed for the first time at the Personal Assessment and Crisis Evaluation (PACE) clinic (9) in Melbourne, Australia.

McGlashan's group (10,11) at Prevention through Risk Identification, Management and Education (PRIME) has reoperationalized UHR criteria, which they called CHR (Clinical High Risk), and has recently advanced the nomenclature of "Psychosis Risk Syndrome" (12). One or more of three criteria had to be met: 1) new onset or recent worsening of subsyndromal ("attenuated") positive psychotic symptoms (APS), 2) very brief periods of fully psychotic positive symptoms (BIPS), or 3) deterioration in functioning within the last year and schizotypal personality disorder (SPD) or a having first-degree relative with psychosis (GRD).

The German Research Network on Schizophrenia, inspired by the theory of Basic Symptoms, has delineated an early initial prodromal state (EIPS) and a late initial prodromal state (LIPS). EIPS is characterized by the presence of at least one cognitive-perceptive basic symptom (COPER criteria) or two cognitive disturbances (COGDIS criteria) in the past three months

and/or meeting the GRD criteria. By contrast, the late initial prodromal state (LIPS) corresponds closely to the APS and BIPS groups outlined above (13).

As readily apparent, the Psychosis Risk Syndromes (PRS) are not based on risk factors *sensu stricto* because none of the criteria, apart from the genetic one, contributes to the pathogenesis of psychosis; however, no criterion determines the subsequent course of illness. Moreover, none of the criteria is a prodromal symptom *sensu stricto*, since in that case they would be epiphenomena of a pathogenesis that moves inexorably from a known *noxa*.

Rather, they are clinical indicators of illness progression, as in the medical model of clinical staging. In this model, proposed by Yung and McGorry (14), each stage of psychotic illness may be characterized by a set of diagnostic assessments based on elements of different nature, i.e., historical, psychometric, neuroanatomical, neuropsychological, pertaining to social and role functioning, and neurobiological, in general, extending to the molecular level. In this model, letting aside prediction, each disease stage could benefit from specific treatment (15).

Transition rates, when the criteria for prodromal syndromes are satisfied, vary across studies; they are currently estimated to be around 30-35% (16,17) at the 28- or 30-month follow-up, respectively. At an 18-month follow-up, combining both UHR criteria and Basic Symptoms (COGDIS), they are around 23%. Prediction models including positive symptoms, bizzarre thinking, sleep disturbances, schizotypal disorder in the patient, level of functioning in the past year, and years of education, or others integrating neuropsychology and neuroimaging data, yielded positive predictive values about 85% (18-20). A 4-level prognostic index classifying the general risk developed by Rurhmann et al. (19) predicts instantaneous incidence rates of up to 85% and allows for an estimation of time to transition. Prediction models and prognostic indexes are mathematical and theoretical; they are not based on longitudinal observation.

The emphasis on the syndromic definition (12) is a prerequisite for the inclusion of a risk diagnosis in the next edition of the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), in which dimensional and longitudinal aspects of psychiatric disorders will be given more importance. There is much debate on this issue.

The proposal for the inclusion of psychosis-risk in the DSM-V as an axis I disorder, called Attenuated Psychotic Symptoms Syndrome (21) or Psychototypal Disorder (22), is based on issues emphasizing the high level of suffering associated with this clinical condition, not otherwise classified, and the need for standardized, guideline-led intervention.

The large number of false positives (despite false negatives appear to be small in number, but lack systematic investigation), methodological limitations, like small number of samples, different selection criteria, no control groups, and heterogeneity of the psychosis transition threshold (23), and the need to increase predicitivity integrating biomarkers, are the issues underlying the more conservative attitudes expressed within the scientific community (24).

Of note, the "psychosis-risk" construct, as currently formulated, is dimensional, rather than categorical. This is in line with one of the main aims of the DSM-V.

Its dimensional nature is betrayed by the difficult compromise between sensitivity, specificity and predictive value of the variables significantly associated with psychotic transition, by the inclusive features of its proposed criteria, and consequently by the assessment to carry-out. Finally, it is confirmed by the outcome of UHR; diagnoses at conversion (a total of 35% at the 30-month follow-up) are schizophrenia-spectrum psychoses in 56% of cases undergoing transition, affective psychoses in 10%, and other psychoses, mainly psychosis not otherwise specified (NOS), in 34% (17).

As it is, the construct defines a risk dimension across traditional nosological categories, which shows a continuum phenotypic expression; the prognostic value of this dimension may not always reach statistical significance and may not apply to all cases, but it may help us understanding the psychopathological issues of individual patients.

The question of translation into clinical care is of relevance, considering that the results of clinical trials with atypical antipsychotics, to test their effectiveness in prevention, did not yield significant evidence for drug treatment. However, evidence obtained with very low iatrogenic index agents (glycine, omega-3 fatty acids) and psychotherapy is more promising.

In other words there is no evidence-based effectiveness for early interventions in the psychoses.

One of the major issues is the increasing difficulty in detecting "true positives", even in academic settings (25). In the community, mental health workers are not adequately trained for the moment to carry-out comprehensive assessment, so the issue is even more prominent; this may partly explain the increasingly higher false positive rate. Hence, it is premature to propose the inclusion of a high-risk for psychosis category in the DSM-V since adequate field and controlled trials are currently lacking. The eventual inclusion must await adequate training of the involved investigators and data gathering.

Before translating the concept of a clinically identifiable PRS into clinical practice, additional research is needed on the accuracy of utilizing currently employed research assessments and criteria in real-world clinical

settings. The predictive power of specific symptoms, symptom constellations, and biomarkers for the development of psychosis in both research and clinical samples needs to be evaluated. The risks and benefits of possible phase-specific treatment strategies have to be determined and the degree of potential harm needs to be weighed against the amount of risk for conversion to psychosis (26).

In clinical practice, despite much dispute as to whether duration of untreated psychosis (DUP) is important or not for the patient's general outcome, we could reasonably settle for reducing it, independently from the question whether it prevents or merely delays the onset of psychosis; extending by even a short time the wellness period of a human being is a desirable goal.

The current scientific debate on early diagnosis and intervention in the psychoses provided new impulse for understanding their pathogenesis, involving the integration of many branches of neuroscience, like neuropsychology and neuroimaging. Consequently, its relevance for clinical care consists in spreading a new psychopathologic culture of the initial stages of psychiatric illness. We may briefly infer that neuropsychological changes related to abnormal neurodevelopment may be perceived as subjective disturbances (i.e., COGDIS) and impair general functioning and sociability. Later, when disturbances worsen and disease progresses, positive symptoms arise. By paying attention to the PRS and to the first signs of a psychosis we may better frame neurocognitive deficit, basic symptoms, negative and positive symptoms into an integrated model, we may better understand what is going on in our patients, and intervene timely to reduce the personal and social impact of this group of mental disorders.

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