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ASSESSMENT AND TREATMENT OF THE RISK OF PSYCHOSIS IN ADOLESCENTS – A REVIEW

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SUMMARY

Background: *When psychosis first presents, and particularly in the case of schizophrenia, the guidelines recommend rapid institution of treatment with atypical antipsychotics. Two different clinical pictures can be observed: psychoses with acute onset and those with insidious onset. Acute cases (60% of the total) have a favourable course in 85% of young patients but where onset is insidious and the symptoms are predominantly negative, the course is poor in 25% of subjects. Since acute symptoms are relatively easy to diagnose, it is diagnosis of the "insidious/negative" cases that represents a major challenge. Is such a diagnosis possible yet? How can we limit the number of false negatives and false positives with the attendant risk of stigma? What treatment should be administered?*

Methods: *Review of the literature (PubMed, PsycARTICLES, PsycINFO) and comparison with clinical practice here.*

Results: *Young people with a high risk of developing psychosis can be identified using scales such as SOPS (Scale of Prodromal Symptoms), PACE (Personal Assessment and Crisis Evaluation) or from the presence of neuroanatomical and genetic characteristics. Unfortunately, these tools are more specific for positive symptoms, and therefore identify a sub-population of young people at risk: those at Ultra-High Risk (UHR). It can be argued that effective treatment is available for these UHR young people to prevent the condition from developing into schizophrenia. On the other hand, the problem persists for young people presenting an insidious onset and predominantly negative symptoms: to date we have no real way of either screening them or assessing the efficacy of a treatment.*

Conclusion: *"Ultra-High Risk" patients are starting to represent a separate nosological entity. This entity is made up of young patients, most of whom have positive symptoms. If left untreated, the course will lead to seriously compromised social and psychological functioning. Rapid diagnosis and treatment for UHRs is therefore essential. In the future we need to refine our diagnostic tools to make them sufficiently specific and sensitive but also so that the widest category of "Risk Syndrome for Psychosis" includes young patients with mostly negative symptoms.*

Key words: *adolescence – ultra-high risk – UHR – psychosis – schizophrenia*

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INTRODUCTION

Psychotic disorders affect 1.2% of the European population aged between 18 and 65 years, with a one-year prevalence of 3.7 million people. Psychoses are one of the most costly diseases for society and are the most disabling; worldwide, in the 15-44 year age range, schizophrenia is the 8th leading cause of disability-adjusted life years (Schultze-Lutter et al. 2008, Rössler et al. 2005). Because there is a peak of prevalence around 18 years, psychiatrists have always been keen to make an early diagnosis and therefore give early treatment. Even today we do not know all the determinants for the prognosis of adolescent psychosis, but we do know that one of them is the type of onset: there is a different prognosis for acute-onset and insidious onset schizophrenia. In 1994, Remschmidt et al. (1994) demonstrated that, for young patients hospitalised for schizophrenia with positive symptoms (type I), the outcome in 40% of cases was remission while 30% developed into a form with negative symptoms (type II). Conversely, in type II, the course was markedly less favourable, with only 2% of young patients going into remission (Figure 1).

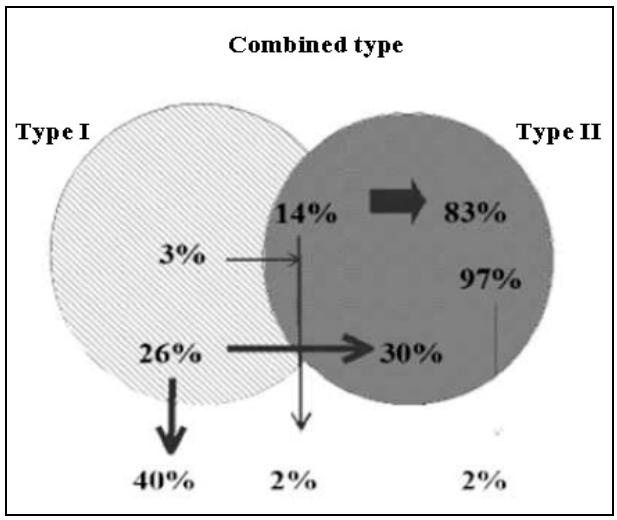

Figure 1. Medium-term course by the type of schizophrenia (Remschmidt et al. 1994)

These gloomy prognoses have, however, since been moderated by data from the study by Harrison et al. (2001), which showed that only 40% of cases had a negative onset and that only 25% of these patients had a poor prognosis (Figure 2).

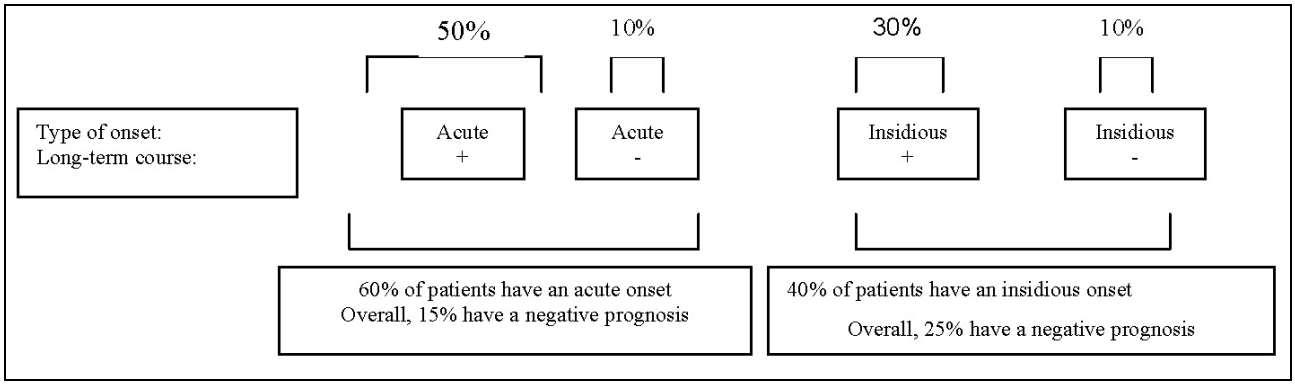

Figure 2. Long-term course by type of schizophrenia (Harrison et al. 2001)

The prodromes for schizophrenia were initially defined as "early, premonitory manifestations of the magnitude of the disorder just before specific symptoms occur". In the main, these prodromes were identified retrospectively. Recent studies have attempted to identify truly prospective criteria. Taken together, these criteria constitute the "Risk Syndrome for Psychosis" (Woods et al. 2009), which is instructive in clinical use. Its increasing importance for the prodromal phase and for prevention arises from various factors:

- several symptoms of the prodromal phase are incapacitating and can themselves lead to long-term disabling and stigmatising dysfunction;
- the existence of disability in the early stages reduces the chances of remission, as shown by studies on the negative influence of delaying treatment for psychosis (Schultze-Lutter et al. 2008, Marshall et al. 2005, Perkins et al. 2005, Fusar-Poli et al. 2009);
- preventive treatment could reduce the incidence of structural brain abnormalities and neurobiological changes (Nelson et al. 2008).

The ability to detect and treat the precursors to psychotic episodes therefore represents a major challenge that would lead to significantly reduced severity of psychotic disorders (Schultze-Lutter et al. 2008). Since second-generation antipsychotics are easier to administer and have fewer undesirable effects (Zdanowicz et al. 2008) they would be particularly indicated in these cases. We are now faced with two questions:

1. Do the tools for early diagnosis currently available to us sufficiently limit the number of false negatives and false positives without the risk of further stigma from the use of antipsychotics (Mees et al. 2011)?
2. For a first established schizophrenic episode, the guidelines recommend treatment, preferably in a depot formulation, administered for at least one year (Zdanowicz et al. 2006). Should the same be done for adolescents with a Risk Syndrome for Psychosis?

METHODS

Review of the literature using the PubMed, PsycLIT and PsycINFO data bases to find clinical research, systematic review and meta-analyses carried out on the early detection and treatment of the prodromal phases of psychosis.

RESULTS

Possibilities of early diagnosis

The criteria first used for early diagnosis were the negative symptoms of schizophrenia, included among residual symptoms in DSM III R (the first 6 items in a list of 9 (Zdanowicz et al. 2002)) (Table 1).

Table 1. Residual and prodromal symptoms as per DSM III R

1. Marked social isolation or withdrawal
2. Marked functional impairment
3. Markedly peculiar behaviour
4. Impairment in personal hygiene and grooming
5. Blunted or inappropriate affect
6. Lack of initiative, energy or interests
7. Digressive speech
8. Odd beliefs or magical thinking
9. Unusual perceptual experiences

While studies to validate these symptoms as prospective criteria came to nought, they did nevertheless reveal that the symptoms had a more frontoparietal origin and that there was an association with male gender and low IQ at remission (Tamminga et al. 1998). The existence of these negative symptoms at an early stage has become a criterion for the severity of the disorder and the level of overall functioning post-crisis (Moller et al. 2000). Conversely, when these symptoms appear late it is difficult to know whether they are of any prognostic value, particularly because it is then difficult to differentiate them from the side effect of the antipsychotics, or from a depressive psychosis. With the failure of this attempt based on purely negative symptoms, research has been refocused on the predictive value of positive but attenuated symptoms. Subjects identified by this method are diagnosed as "Ultra-High Risk". Two attempts to standardise these criteria gave rise to the SOPS and PACE scales:

- SOPS (Lencz et al. 2003) (Scale of Prodromal Symptoms) is a scale with 4 main classes of symptoms: 5 positive items, 6 negative items, 4

disorganised items and 4 items measuring general symptoms. SOPS rates symptoms quantitatively on a scale from 0 to 6. A subject with a score of between 3 and 5 on any subscale will be identified as "at-risk" and a score of over 6 indicates a probable psychotic condition.

- The first studies using PACE (Personal Assessment and Crisis Evaluation) (Schultze-Lutter et al. 2010, Nelson et al. 2008, Fowler et al. 2010) showed that UHR subjects have a rate of transition to psychosis of between 35 and 54% over 12 months. Unfortunately, more recent studies have reported lower rates – between 20 and 35% (Yung et al. 2007, McGorry et al. 2008, Cannon et al. 2007). Various explanations have been given for these disappointing new results: the efficacy of early detection of UHR patients and treatment administered to them, larger samples leading to a statistical dilution and thereby a larger number of false positives (Table 2).

Overall, these scales are thought to predict a 30-35% risk of developing frank psychosis within the subsequent year or two. This level indicates a markedly higher risk than the risk of psychosis in young people in the general population (Cannon et al. 2008).

In 2009, a wide-ranging longitudinal study in North America showed that 40% of the 377 subjects tested with the SIPS (Structured Interview for Prodromal Syndromes) and identified as being UHR suffered from a frank psychotic disorder during the 2½-year follow-up period. The sensitivity for conversion to psychosis was 89%, with a specificity of 60.2% (Woods et al. 2009). As a result of this limited specificity, symptoms considered more "basic" (Basic Symptoms Criteria: BSC) (Koch et al. 2010, Velthorst et al. 2009) have been added to the prediction algorithms. The results with these added criteria seem promising, with an improved predictive power for the annual conversion rate of up to 68-80%, compared with 40% for the SIPS when used alone (Cannon et al. 2008) or compared with 25% for the BSC alone (Koch et al. 2010). It should, however, be noted that the low predictive value of the BSC in the first year is compensated for in subsequent years by a 70% conversion rate in 100 patients followed up for 9.6 years, and an average conversion period of 5.6 years (Nelson et al. 2008) (Table 3).

Table 2. Personal Assessment and Crisis Evaluation (PACE) criteria

Require that a young person, aged between 14 and 30 years, who have a perceived need for care, meets criteria for one or more of the following groups:

- Attenuated Psychotic Symptoms (APS): have experienced attenuated positive psychotic symptoms (Magical thinking, paranoid ideation/mistrust, unusual perceptual experiences, body-related illusions, idea of reference…) during the past year.
- Brief Limited Intermittent Psychosis Symptoms (BLIPS): have experienced episodes of frank psychotic symptoms, no longer than a week, with spontaneous full recovery.
- Combination of Risk Factor (have a first degree relative with a psychotic disorder or meet diagnosis for schizotypal personality disorder) and Recent Functional Decline during the past year.

Table 3. The Basic Symptoms Criteria

Cognitive Perceptive Basic Symptoms (COPER): At least one of the following basic symptoms with at least weekly occurrence within the last 3 months + first occurrence at least 12 months ago:

- thought interference;
- thought perseveration;
- thought pressure;
- thought blockages;
- disturbance of receptive speech;
- decreased ability to discriminate between ideas and perception, fantasy and true memories;
- unstable ideas of reference;
- derealization;
- visual perception disturbances;
- acoustic perception disturbances.

Cognitive Disturbances (COGDIS): At least two of the following basic symptoms with at least weekly occurrence within the last 3 months:

- inability to divide attention;
- thought interference;
- thought pressure;
- thought blockages;
- disturbance of receptive speech;
- disturbance of expressive speech;
- unstable ideas of reference;
- disturbance of abstract thinking;
- captivation of attention by details of the visual field.

Table 4. ARMS-E and -L classification: Individual With ARMS Without APSs and/or BLIPSs

ARMS-E: Individual With ARMS Without APSs and/or BLIPSs
1. Cognitive Perceptive Basic Symptoms (COPER) 2. and/or 3. Reduction in Global Assessment of Functioning Scale score (DSM-IV) of ≥ 30 points (within the past year) combined with ≥1 of the following trait markers: ▪ First-degree relative with lifetime diagnosis of schizophrenia or a schizophrenia spectrum disorder; ▪ Prenatal or perinatal complications.
ARMS-L: Individual With ARMS With or Without Basic Symptoms, With or Without Global Functioning and Trait Markers
1. Individuals had ≥1 of the following APSs within the past 3 months, appearing several times per week for a period of≥1 week: ▪ Ideas of reference.

Another way of increasing the sensitivity of the scales is by cross-validation with MRI findings. In this regard, Koutsouleris et al. (2009) predicted the risk of transition by associating patterns of neuroanatomical abnormalities observed on MRI.

There is some uncertainty as to which of these scales is the earliest indicator. Some authors consider that BSC offers the most sensitive scale for predicting Attenuated Psychotic Symptoms (APS) and Brief Limited Intermittent Psychotic Symptoms (BLIPS) using the ARMS classification (At Risk Mental State – CAARMS (Comprehensive Assessment of the At Risk Mental State)) of the psychosis and its early (-E) and late (-L) subtypes (Table 4). This point of view was not, however, confirmed by a German retrospective study in 2010 (Shultze-Lutter et al. 2010).

Treatment

While matters such as the choice of medication strategy, and even whether medication should be given, are open to discussion, all authors now consider psychoeducation to be a sine qua non. As well as having no side effects, it has the advantage of having objectives that can be adapted to the phases of the psychotic disorder. It can range from "simple" psychoeducation to more "therapeutic", systemic/family-based objectives. In this regard, Schiffman et al. (2002) showed that, in the "at-risk" stages, having positive relationships with both parents can protect against the development of schizophrenia. In 2004, Morrison et al. (2007) went further, demonstrating in a 6-month study with 58 UHR patients that there was a 15% reduction in the conversion rate when monthly follow-up with CBT was given. This benefit proved stable over the following 3 years. In another study in 2006, 79 at-risk subjects were randomised into either an integrated treatment arm (with self-affirmation, social skills training and family psychoeducation segments) or a standard treatment arm, provided in a clinic. Two-year follow-up revealed a 25.0% conversion rate for integrated treatment compared with 48.3% for standard treatment (Nordentoft et al. 2006).

At "established" stages, although psychosocial intervention with or without family-based treatment did not reveal any marked improvement in prognosis, it did nonetheless prove effective in reducing the number of hospital admissions. This effect was due to an increased level of treatment compliance and greater tolerance of symptoms by family members (Lenior et al. 2001).

Medical intervention

Since not all UHR subjects develop psychosis, there are two requirements to be met when prescribing medication (McGuire 2003):

- first, the treatment should alleviate symptoms, the patient's current difficulties and in particular the risk of developing psychosis;
- secondly, because specificities and sensitivities are still unreliable, inappropriate and therefore unnecessarily stigmatising prescriptions should be avoided.

Because of this, the place of antipsychotics is still being debated and alternative treatments are being proposed.

In this connection, 1st generation antipsychotics have now been practically abandoned. The seminal study supporting atypical antipsychotics is by McGorry et al. (2002). The authors selected high-risk subjects aged 14-28 years and treated them by psychotherapy, associated in some cases with 1-2 mg risperidone, for 6 months. Follow-up was given for one year. While the same proportion of patients treated with psychotherapy "alone" had a negative course as those under "psychotherapy + risperidone", the authors observed that where patient compliance with risperidone was good the risk of a negative course diminished over the 6 months of treatment. Unfortunately, the two types of psychotherapy were not comparable, since that used in the "with risperidone" group was more specific for psychotic problems. In a recent meta-analysis, Kelly et al. (2010) showed that there was about a 15% reduction in the transition rate solely with risperidone and amisulpride (McGorry et al. 2002, Ruhrmann et al. 2007). As for the results with olanzapine, they were at the limit of statistical significance (McGlashan et al. 2006). No serious study has been conducted to date on aripiprazole (no control group in the study by Woods et al. 2007). From the point of view of side effects: 81% of patients

treated with amisulpride had elevated blood prolactin levels (Ruhrmann et al. 2007), 61% of patients on olanzapine experienced weight gain (McGlashan et al. 2006), 60% of patients receiving aripiprazole suffered from akathisia (Woods et al. 2007) and 12% of patients on risperidone reported stiffness (McGorry et al. 2002).

Apart from the use of antipsychotics, some antidepressants and long-chain omega-3 fatty acids have been tested (Thibaut 2014). For instance, Cornblatt et al. (2007) treated 20 UHR patients with second-generation antipsychotics versus antidepressants and could not reveal any difference in efficacy; however, there was a higher drop-out rate in the antipsychotic group. In 2010 Amminger et al. (2010) used omega-3s in a 52-week randomised study. They demonstrated a 22.6% reduction in cumulative risk in the omega-3 group. Omega-3s also proved effective in reducing positive, negative and general symptoms and in improving overall functioning (De Koning et al. 2009) without any increase in side effects (Berger et al. 2007) compared with placebo.

DISCUSSION

Although it is relatively easy to diagnose acute-onset schizophrenia because of the florid nature of its symptoms, at least 40% of disorders have a gradual, insidious onset. This form of schizophrenia has a poorer prognosis. The efforts of psychiatrists have therefore focused on early diagnosis of these disorders. It is instructive to note that researchers were initially interested in being able to identify schizophrenia with negative, insidious symptoms and that, as research progressed and particularly in view of the failure to identify these young patients, positive symptoms featured more and more in the diagnostic criteria for at-risk subjects: UHRs (Woods 2010, Shrivastava et al. 2011). The specificity of negative symptoms is still low either because it is difficult to find adolescents that do not recover "normally", for varying periods, from two or three of these symptoms at the same time, or because these symptoms closely resemble depression (Zdanowicz et al. 2006a). In view of this, De Clercq & Peuskens (2000) showed, as early as the first decade of the new millennium, that it took at least 5 years to confirm a diagnosis of schizophrenia, and Werry (1992) and Vazquez-Barquero et al. (1996) have also discussed at length the relevance of schizophrenia symptoms in adolescence, particularly the relevance of negative symptoms. Finally, since the pharmacological studies available to us deal mainly with UHRs, we can ask what therapeutic approach should be adopted for a young person with only "negative pre-symptoms".

CONCLUSIONS

"Ultra-High Risk" patients are starting to represent a separate nosological entity. This entity is made up of young patients, most of whom have positive symptoms. If left untreated, the course will lead to seriously compromised social and psychological functioning. Rapid diagnosis and treatment for UHRs is therefore essential. In the future we need to refine our diagnostic tools to make them sufficiently specific and sensitive but also so that the widest category of "Risk Syndrome for Psychosis" includes young patients with mostly negative symptoms.

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