ETHICAL ISSUES RELATED TO EARLY INTERVENTION IN CHILDREN AND ADOLESCENTS WITH ULTRA HIGH RISK FOR PSYCHOSIS: CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

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Abstract

The ethical considerations in child and adolescent psychiatry are highly complex and of great interest nowadays. Early intervention involving persons at risk for psychosis puts some ethical debates to the forefront. When applying early intervention in children and adolescents with psychosis UHR-ultra high risk, we must be careful to respect the ethics principles. The procedural ethics implies the fact that early intervention may be employed if it poses minimal risks and offers a direct medical benefit. Our research was performed between 2004 and 2014, involving high-risk children, who were offspring of psychotic parents and 105 psychosis UHR children. Our particular interest was to apply a proper intervention in an ethical framework and to evaluate the transition of UHR individuals to diagnosable psychosis in a given period of time. Our main focus was to investigate which types of intervention strategies would be most indicated and ethical for the UHR population in order to prevent or postpone the transition to psychosis. Our results, showing statistically significant differences between the patient treatment groups, sustain that targeted needs-focused therapy and extensive psychosocial interventions can prevent the transition to psychosis, bringing benefits for the patients. The early intervention in an ethical framework might be of top importance in protecting the children’s development, being highly unethical not to intervene and possibly neglect the high needs of this vulnerable group, but the intervention should begin with the most benign treatment administered at a very early stage of the illness.

Keywords: research ethics, early intervention, psychosis, minors, ethical frame

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Introduction

The ethical considerations in the field of child and adolescent psychiatry are highly complex and of great interest nowadays. In recent years, the psychiatric ethics has increasingly captured the public attention, mainly because of the ethical controversies, debates and dilemmas. Although, the psychiatric research offered lately a great promise for the future, a profound awareness of the related ethical issues developed in time [1-3].

The application of the medical prevention model, although a valuable pathway in the health problems management, raises a variety of ethical issues in psychiatry [1, 4, 5].

Early intervention involving persons at risk for psychosis (schizophrenia, affective psychoses) puts some ethical debates to the forefront. When the clinical psychiatric issues and research involve children and adolescents, the problematic is much more sensitive, with special vulnerabilities and sensitiveness, which justify heightened ethical concerns [6, 7].

When addressing those issues of ethical complexity in early intervention involving children and adolescents at risk for psychosis, the need for optimal procedures to protect those subjects is evident. In the same time, the involvement of children in research, being a great challenge concerning the ethical issues, the relevant international ethics guidelines for the research involving minors must be respected [5, 6, 8].

When applying early intervention in children and adolescents with UHR-ultra high risk, we must be careful to respect the ethics principles: the patient’s right to be protected from harm, the ethical human values, the risk-benefits approach. There is an ethical need to respect the privacy of the patients and the confidentiality of the personal data [9].

The procedural ethics implies the fact that the early intervention may be employed if it poses minimal risks, offering a direct medical benefit and the risk-benefit ratio should be acceptable. It would be ethical, if the early intervention could ameliorate or possibly prevent the onset of the disorder [5, 8, 10-14]. In the same time, it is very important to minimize the risks of stigmatization and self-stigmatization [15].

Some existent studies prove a 35% conversion to psychosis, without a targeted intervention and a 10% conversion with applied interventions (pharmacotherapy, psychosocial interventions), after 1 year. This means that the conversion to psychosis could be prevented in 2/3 of the patients, the benefit being evident [16-18].

Benign techniques like supportive psychotherapy and psychosocial interventions can be helpful to the patients and produce no harm, being ethical and minimally invasive. The close monitoring of the patients allows a very rapid detection and treatment for the patients who convert to diagnosable psychosis [19, 20].

The studies in this field of early intervention in UHR children and adolescents proved that some developmental, early precursors of the psychosis onset are detectable. This is why the evaluation of the premorbid functioning is essential and constitutes a base for the early detection and intervention initiatives [21-24].

The investigation of the vulnerability markers in the high risk population is of high interest, because it can bring information concerning the
biological and environmental causes of psychoses. Both schizophrenia and bipolar disorder are heritable, a high rate of those diagnoses being found in the offspring, and for this reason it is important to know the psychiatric family history for the UHR-ultra high risk patients [25-30].

The best predictors of conversion to psychosis were the poor premorbid adaptation, functioning during childhood, the long duration of untreated symptoms and the presence of pregnant negative symptoms.

Some retrospective studies have shown that frank psychosis is often preceded by a syndrome which often consists of comorbid nonspecific symptoms, including depression, social anxiety, suspiciousness and social withdrawal, conduct disorders, attention deficit and functional impairment [19, 31].

The prospective studies showed that the psychopathologic phenomenon has its origin not only in the genetic-bio-chemical individual structures, but also in the interaction mechanisms with the environment. Naturally emerge the questions: what environmental factors interact with the genetic predisposition, which are the real risk factors and the helpful early intervention strategies. The clinical reality proved that some children can show better resilience mechanisms and don’t develop a psychopathology, and this is why the intervention should be focused on enhancing the resilience, because this is a dynamic variable.

The chronic illness course, the progressive grey matter decline during early disease stages formed the basis for the research on the Psychosis Risk Syndrome (PRS) known as “Clinical High Risk” (CHR) or “Ultra-High Risk” (UHR) or Prodrome [21].

Different research diagnostic instruments have been used to identify different types of Psychosis Risk Syndromes: Brief Limited Intermittent Psychotic Syndrome (BLIPS); Attenuated Positive Symptoms Syndrome (APSS) and Genetic Risk and Deterioration Syndrome (GRDS) [20, 23, 26-30].

It was suggested that the presence of significant, attenuated negative symptoms is associated with higher rates of conversion to psychosis [21].

P.R.S (Psychosis Risk Syndrome) indicates a potential risk for psychosis based on a constellation of symptoms and signs, differentiating it from the genetic or family high risk research.

The early appearance of functional decline is of particular importance for the overall severity and impact of the disorder due to the young age at which it can occur, especially in children and adolescents.

Progressive brain changes have been documented in PRS individuals who convert to psychosis compared to those who did not convert to psychosis [21, 24].

The presence of more or less behavioural and cognitive abnormalities in children who later develop psychosis point to the influence of early neurodevelopmental disturbances, built on the underlying brain vulnerability. This could lead to increased grey matter loss and increased neurodegenerative processes.

The transition to psychosis is not inevitable or predetermined in individuals who meet current at-risk criteria: there is a 35% chance of developing a different psychiatric disorder and a 29% chance of having no diagnosable condition after 1 year. In genetic high-risk studies the risk of psychosis has been found to be 10%-

66
20% [18, 25, 32].

Some valuable studies reported a rate of transition to psychosis in the UHR patients of 41% by 12 months and 50% by 24 months [26, 27]. Other significant studies suggest a conversion rate to psychosis of 64% in the UHR patients [25].

The serious impact that psychosis (schizophrenia- and affective spectrum disorders) has on a person’s psychosocial, educational, vocational functioning and on the quality of life makes early prevention an urgent goal [21, 23].

More complex problematic cases are found in areas of social disadvantage, lack of local care policies, so that a major service reorganisation may be required to meet the needs of the UHR patients [19].

The clinical and research implications of this field of research on UHR patients, intersect in several ways with ethical considerations. There emerge key ethical considerations regarding the treatment of patients thought to be at high risk for developing psychosis. When a patient presents with characteristics of prodromal symptoms of psychosis, the clinician has to consider the intervention by assessing the demographic, clinical and familial risk for the disorder.

Several clinical and ethical dilemmas arise when treating the children and adolescents. Those ethical issues are multifaceted: early intervention could determine some stigmatizing valences and the awareness of being identified as vulnerable for a serious psychopathology [21, 32, 33].

The participation in a research study involves specific risks and benefits for the UHR patients, who meet criteria for at-risk mental states [34].

The risks include those associated with being identified as vulnerable for a disorder that may never develop (anxiety, discrimination from others) and the risk of receiving unnecessary medication that may cause unwanted side effects.

On the other hand, major potential benefits of research participation include the possibility of receiving early and effective treatment, should a disorder develop and the possibility that the treatment could reduce distress from the prodromal or at-risk symptoms per se. Another ethical issue would be that the informed consent for prodromal research participation is based on the assumption that the subject is competent. Some candidates for prodromal research may not meet the standards of competence because of cognitive deficits, unusual thinking processes, or no insight and denial of the existent psychiatric illness [34, 35].

The fact we are dealing with UHR children introduces additional ethical complexities. It is very important to know all these risks in order to evaluate the situation objectively and accurately. This is why, the ethical principles, the evidence based information, the legal context, the developmental considerations and the clinical context relevant for each situation must all be integrated in the consultation with children and adolescents and their parents in order to achieve an adequate treatment plan [5, 8].

The mental health treatment for children and adolescents is usually delivered within the context of the family, with the support of the parents. The family and the psychosocial interventions (case management, close
monitoring and crisis response, cognitive-behaviour therapy, family support and education) are significant and could bring positive results. Sometimes, there are developmental factors that affect the ability of children and adolescents to make their own treatment decisions, so they need clear information and psycho-education.

The research may provide answers about how and when to treat prodromal patients [26, 35].

The logic of early intervention is partly based on accessing individuals in a more treatment responsive stage of illness in which the psychosocial, developmental and cognitive damage is less extensive and partly on remediating an active process of progressive neuro-destruction that leads to pathophysiological symptomatic and irreversible structural changes.

The risk-benefit analysis of medical treatment is more complex and suggests that there are a number of variables that confer some indications of vulnerability to psychosis, which are compulsory to be taken into account. It is ethical to determine who is a suitable candidate for early intervention, respecting the existing, clear criteria, and applying them with precision. This could make the possibility of false positives much lower [10, 31].

It is known that treating the susceptibility to a disorder can be more complicated than treating the disease.

The inclusion of prodromal cases, formally within diagnostic systems provides a consensus judgment that this group has needs which require independent recognition as an illness. The most indicated approach is offered by the diagnosis clinical staging as an alternative to an ethical approach of early prevention in psychiatry [11]. This suggests that there may be stages in the evolution of psychotic disorders, which become more specific in the evolution to more concrete disorders.

According to some evidence based researches, the early interventions and treatment proved to be effective in delaying or preventing the onset of psychosis, then a just waiting attitude could be regarded as non-protective and unethical. Some international service models have been developed to manage the existent issues ethically and with considerable clinical sensitivity [35].

**Materials and Methods**

Through our research, which offered an ethical frame to our daily clinical practice with children and adolescents with psychosis risk syndrome, we respected the procedural ethics, a notice of acceptance from the ethics committee being obtained.

We considered the ethical foundation of our research complied with the principles related to the child’s rights, to the respect of the human dignity, the freedom of choice, the right to be informed and tried to solve any possible ethical issues occurring from the nature of research. In the same time, one of our aims was to ensure the confidentiality and protection of data concerning this vulnerable paediatric population.

The prospective research was performed at the University Hospital of Psychiatry and Neurology for Children and Adolescents in the period 2004-2014, and involved genetically high-risk children, who were offspring of psychotic parents (95 children with parents suffering of schizophrenia and 98 children with parents with bipolar disorder) and 105 UHR-ultra high risk
children. We identified the genetically high risk children from help-seeking families with one or both psychotic parents having offspring who needed care in our clinic at that time. The UHR-ultra high risk for psychosis children were also referred to our clinic because of their existing psychopathology.

For each patient under 18 years we obtained the informed consent from the parents/legal guardians and the assent from the child and when the patients turned 18 years we obtained the informed consent signed by them. Our research is in accordance with the Ethical Committee regulations of the ‘Victor Babes’ University of Medicine and Pharmacy Timisoara and with the ICH-GCP (Good Clinical Practice) regulations and guidelines. Our followed procedures and the research were in accordance with the ethical standards of the original Helsinki Declaration, revised in 2000.

In accordance with the Madrid Declaration of the World Health Organization, the procedures were very precisely discussed with the patients and their families, the consent was accurately informed, voluntary and in written form.

We applied a qualitative strategy and an interactive, dynamic method for obtaining information. The approach included an informed consent through educational methods and interventions that ensure that the research candidates understand the study’s design, the risks and the benefits of participation, the differences between research participation and a personally structured plan of care and the likely consequences of accepting or declining recruitment.

In both groups, with high risk and UHR, the patients were aged between 9 and 18 years, the average age being 13.84 ± 4. The gender percentage in the sample was 59% male / 41% female.

At baseline, we assessed the existent psychiatric symptoms using the BPRS-Brief Psychiatric Rating Scale, the K-SADS-PL (Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version) and the SIPS-Structured Interview for Prodromal Syndromes. We applied: CGAS-Clinical Global Assessment Scale – for the evaluation of global functioning and the CD-RISC (Connor-Davidson Resilience Scale). CD-RISC consists of 25-items that measure the ability to cope with stress and adversity. It was designed to quantify self-reports of resilience and to measure the response to treatment in a clinical population. Each item is rated on a 5-point scale (0-4), where higher scores reflect greater resilience, better adaptability and quality of life.

The SIPS was applied in order to identify the ultra high-risk individuals and to distinguish between the different types of psychotic risk syndromes (PRS).

Through the SIPS, 3 types of psychotic risk syndromes were identified: BLIPS-Brief Limited Intermittent Psychotic Syndrome, APS-Attenuated Psychotic Symptoms group and GRDS-Genetic Risk and Deterioration Syndrome.

Our particular interest was to evaluate the transition of UHR individuals to diagnosable psychosis in a given period of time. Our main focus was to investigate which types of intervention strategies would be most indicated for the UHR population in order to prevent, decline or postpone the transition to diagnosable psychosis.

After explaining the procedures,
the risks and the benefits to the parents and the patients, the UHR for psychosis patients were divided into 3 groups: in G1-33 patients, in G2-40 and in G3-32 patients.

G1 (group 1) received needs-focused interventions, meaning extensive psychosocial interventions plus pharmacotherapy (antidepressants, low dose atypical antipsychotics) for the existent anxiety, depressive, negative or positive symptoms, in accordance with the clinical staging model of the disorder, the clinical evolution and needs. G2 received the support through intensive psychosocial interventions and G3 were under close clinical monitoring for their state and symptoms, in order to receive in case of transition to psychosis, the most appropriate early intervention.

The scales were compulsory applied every 6 months for 3 years by a psychiatrist who was blinded to the information about the treatment group of the patients.

In the genetic high risk group, out of the 95 offspring of parents with schizophrenia, we had 70 with psychopathology and 25 without, respectively for the offspring of bipolar parents, 65 with psychopathology and 33 without. The children without psychopathology in both groups were siblings of those with psychopathology, and lived in the same environment.

For the high risk group we evaluated the CD-RISC resilience scores, partly as the expression of the life quality of these children, at baseline (T1-timepoint1) and after applied targeted intervention strategies (pharmacotherapy for the existent psychopathology and psychosocial interventions), every 6 months till T2-timepoint2- after 3 years. We applied the scales in different time-points in order to evaluate and quantify the efficacy of proper interventions especially concerning the resilience and, as a projection, the implicit quality of life.

Our primary investigation endpoint outcome was the transition to psychosis rate based on the applied interventions in the 3 treatment groups. We also evaluated which factors are important and influential in preserving a good mental health and preventing the development of psychopathology or frank psychosis, through the identification of the most influential vulnerability, candidate predictors and of the crucial protective, resilience factors and processes.

Our whole research was conducted in an ethical framework, trying to respect the rights and needs of the patients and their families, and applying suitable interventions, with the best consequences possible concerning the safety and side effects, in the least restrictive environment and least invasive way. In order to apply the suitable interventions, in an ethical framework, the first step was to diagnose the patients with the proper, known UHR criteria.

We used the Cox regression (a stepwise procedure, the most significant variables being entered individually) to examine the significance and the correlation between some baseline candidate predictors and the transition rate to psychosis. The Pearson correlation test was applied, in order to check for the presence of statistically significant correlations between the CD-RISC resilience scores and the transition to diagnosable psychosis.
Results

The most frequent diagnostic categories of offspring with psychopathology from parents with schizophrenia or bipolar disorder were: obsessive-compulsive disorder, generalized anxiety disorders, social phobia, panic disorders, ADHD - Attention deficit hyperkinesia disorder, conduct disorders, learning disorders, language disorders, tics, elimination disorders and eating disorders.

Concerning the diagnoses of the high risk children we found the lowest CD-RISC scores of resilience for the offspring with generalized anxiety disorders, OCD - Obsessive-compulsive disorder and ADHD, as a marker of low self-efficacy and low self-esteem.

Through the CD-RISC application, we noticed in both groups of children who developed psychopathology, low resilience scores in the main domains. The mean total CD-RISC resilience score for the high risk children who developed psychopathology was 45.5 (standard deviation = 8.7) for the offspring of schizophrenic parents, and 52.8 (sd = 9.4) for the other offspring.

Figure 1 illustrates the mean scores in CD-RISC on the 5 domains coded through the 25 items of the scale for: HRPBPD-high risk children of parents with bipolar disorder, HRPSZ-high risk children of parents with schizophrenia, T2HRPBPD-timepoint2 scores - children of parents with bipolar disorder, T2HRPSZ-timepoint2 scores - high risk children of parents with schizophrenia and for the offspring, without psychopathology.

We evaluated the CD-RISC scores of the high risk children with psychopathology for timepoint1 and after applying proper intervention strategies in timepoint2.
We noticed higher mean total resilience scores (improved from 45.5 to 58.2 for the offspring of schizophrenic parents and from 52.8 to 69.7 for HRPBPD) and on the 5 key domains, reflecting greater resilience in both studied groups after the customized interventions. We noticed that the children without psychopathology in both groups had generally higher mean scores for resilience in CD-RISC, as well as concerning the 5 key factors: tenacity/self-efficacy, strengthening through stress, adaptability, control and meaning. Their mean total resilience scores in timepoint1 were 70.6 for HRPSZ and 74.3 for HRPBPD (sd=10.4).

In their case, the targeted intervention was not applied, and at timepoint2 we found that HRPSZ-25%, and for HRPBPD-30% developed psychopathology and their mean total resilience scores were 57.3.-HRPSZ and 60.1-HRPBPD. These results prove the fact that through proper intervention strategies the transition to psychopathology or psychosis could be prevented in the genetically high risk groups.

Concerning the UHR group, through applying the CD-RISC, in order to evaluate the clinical efficacy of the early intervention, we obtained for the 3 groups - G1 (receiving needs-focused interventions), G2 (receiving intensive psychosocial interventions), G3 (under close clinical monitoring), after 3 years, the following results for the mean resilience scores (Figure 2):

![Figure 2 Mean CD-RISC resilience scores after 3 years for the 3UHR treatment groups](image-url)
Therefore, the highest resilience scores for G1, the group receiving needs-focused interventions, after 3 years, prove the best clinical efficacy, functioning, adaptability and quality of life in this group. Good resilience scores but not so high like for the G1 group, were obtained for the G2 group, who received intensive psychosocial interventions. The lowest resilience scores were obtained by the G3 group.

Concerning the transition rates to diagnosable psychosis in function of the applied intervention strategy in the 3 treatment groups, we observed the following results: after 1, 2 and 3 years-the highest percentage of transition to psychosis for the G3 group – 39%, 48%, 54% and the lowest transition rate for the G1 group with needs-focused interventions -9%, 11%, 15% (Figure 3).

![Figure 3 Percentage transition rates to psychosis for the 3 UHR treatment groups after 1, 2 and 3 years](image)

These results prove the efficacy of needs-focused interventions for the UHR groups. After 1 year, only 9% in the G1 group (receiving needs-focused interventions) converted to psychosis in comparison with 25% from the G3 group.

Also, the psychosis transition rate in the G2 group who benefited from intensive psychosocial interventions was lower than in the G3 group.

These results represent a major step towards preventing or at least postponing the transition to psychosis in the UHR categories.

By applying the Pearson correlations we obtained the following statistically significant negative
correlation between the low resilience scores in CD-RISC and the high transition to psychosis, especially in the G3 group, after 3 years. The resilience being a dynamic variable, in direct correlation with the quality of life of the patients, that can be enhanced, our results prove that through early intervention the transition to psychosis could be prevented, in direct interaction with the resilience mechanisms improvement (Figure 4).

Figure 4 The negative correlation between the resilience scores (CD-RISC) and the transition rate to psychosis

In order to act ethically and prevent as much as possible to choose false positive patients concerning the conversion to psychosis, we correlated some candidate predictors with high predictive power, with the transition to psychosis (Table 1).

Table 1 Cox Regression p values for the correlation between each baseline variable and the transition to psychosis in the UHR group
### Table 1: Candidate Baseline Predictors

<table>
<thead>
<tr>
<th>Predictor</th>
<th>p value</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms</td>
<td>0.000001</td>
<td>0.00021</td>
</tr>
<tr>
<td>CGAS-global functioning</td>
<td>0.000003</td>
<td>0.00043</td>
</tr>
<tr>
<td>CD-RISC resilience scores</td>
<td>0.00004</td>
<td>0.00029</td>
</tr>
<tr>
<td>SIPS Negative Symptoms</td>
<td>0.00001</td>
<td>0.00023</td>
</tr>
<tr>
<td>SIPS Positive Symptoms</td>
<td>0.006</td>
<td>0.017</td>
</tr>
<tr>
<td>Unusual thought content</td>
<td>0.00002</td>
<td>0.00032</td>
</tr>
<tr>
<td>Conceptual disorganization</td>
<td>0.00001</td>
<td>0.00015</td>
</tr>
</tbody>
</table>

The best baseline predictors for the transition to psychosis were: the duration of symptoms till first presentation at the clinic, CGAS-global functioning scores (low scores predictive for transition), CD-RISC resilience scores (low scores predictive for transition to psychosis), the SIPS negative symptoms and the conceptual disorganization of the patient.

According to our statistically significant results, it is obvious that the early intervention in an ethical frame, adapted to the needs-focused approach, brought benefits to the patients, and prevented their conversion to psychosis. At the same time, some favourable results were obtained through the extensive psychosocial interventions.

**Discussion**

In order to act ethically, evidence based research results for best clinical practice in children at-risk for psychosis are needed [11, 35].

The ethical requirements must compulsory be fulfilled for a proper early intervention. The application of ethically obtained research findings should be implemented into the early intervention programs [26, 27].

The psychiatric research developed in an ethical framework should respect the following key features: scientific and patient’s benefits, accurate expertise, commitment, integrity, confidentiality, a proper risk-benefit ratio, informed consent and decisional capacity [1, 36].

The patient should trust the psychiatrist through a good patient-doctor relationship and should be engaged to the selected intervention [37, 38, 39].

It is essential and ethical to engage the patient and his family at an early stage of the disorder, to educate them about the diagnostic, to help them deal with the stigma and to decide collaboratively on the intervention strategy [38].
As mentioned, the risk of treating false positive patients, who, despite the ultra-high risk criteria fulfilment, don’t convert to psychosis in time, is very low if the patients are accurately evaluated with current valid criteria [27]. As current services mainly focus on the issue of addressing the risk of psychosis, ethical issues have been raised about the appropriate management of the false positive cases, which meet the existing criteria but may be at lesser risk. Among these cases there are real fears over stigmatization, labelling, inducing unnecessary fear and the possible side effects of medication. One readily apparent problem for false positives is the risk of over-treatment [10, 31]. They present symptoms and distress that with current criteria could not easily be differentiated from those who do convert to psychosis [26-30]. On the other side, it is possible that being identified as at-risk early in the progression of the illness may decrease the transition rate, thereby creating a subgroup of false-negative patients [24].

The intervention and treatment research in the prodrome appears to be justified, but the length of treatment that is required to prevent psychosis indefinitely needs to be individualized and further research in an ethical framework should be done [27]. It is important to evaluate accurately which children will respond to what intervention type. This is why an individualized, tailored therapy is more and more needed.

In the clinical setting, genetic testing for susceptibility and for drug metabolism and response is just beginning to be applied in psychiatry and could be a valuable key for personalized, tailored pharmacotherapy adapted to the needs of the patient, this being an ethical attitude towards future perspectives [40]. The pharmacogenetics could create the premise for choosing the most appropriate treatment, respecting the ethical, safety and efficacy aspects [41, 42].

The ethical principles of benefit and no harm suggest that careful attention must be paid to the psychological, psychosocial effects of psychiatric genetics, in order to maximize the personal benefits and to minimize the risks.

Psychiatric genetics brings a complexity of ethical considerations, derived from the significant relationship between the genetic information and the further mental health of the person, as well as the psychosocial consequences. Psychiatric genetic research is a source of great hope for many individuals with mental illness, their families and the clinicians who care for them but it should be done in an ethical frame and setting, in an non-stigmatizing climate. Molecular genetic variants associated with bipolar disorder, major depression and schizophrenia have been validated in independent samples and researches.

The psychiatric genetics describes an emerging group of clinical applications such as pharmacogenetics, diagnostic and susceptibility genotyping. There is a need of future ethical genetic counselling and testing in psychiatry [41, 42, 43].

A multidisciplinary approach to clinical care, involving both psychiatrists and genetic counsellors has been suggested [43].

The psychiatrists, the geneticists, social scientists, bioethicists and clinicians in general will be challenged, to look for new ways to
collaborate and to learn more about the true risks and the benefits of the genome era in psychiatry.

There is a complex interplay of biology, genetics, medicine, psychology, sociology and ethics in this issue of the psychiatric field, so that a multidisciplinary approach is essential. The issue of prevention can then be explored with respect to the longer term outcomes of effective treatments, in an ethical setting.

Individuals with a 40% risk of psychosis have the right to know their risk. Counselling about the probability and the uncertainty of prediction needs to be offered in a sensitive, ethical way [26, 27].

In order to act ethically, we analyzed the benefits of early interventions. The benefits of intervention include: reducing symptoms, delaying psychosis onset and intervening during a time when the patient keeps a level of insight that may allow for establishment of trust with mental health professionals and improved adherence to treatment [24].

One possible way of increasing the predictive power of current methods is to identify the brain based neurobiological markers that point out the vulnerability for psychosis [11, 12, 16, 33].

A number of potential endophenotypes for psychosis, including psychophysiological, neurocognitive and neuroimaging measures have shown promising preliminary results in predicting later psychosis. The rapid advances in the field of genetic markers can assist in predicting subgroups at risk for psychosis.

The concurrent goal of our research team was to enhance positive aspects of the patients’ and their families functioning, even in families living under high risk conditions.

This contextual approach - process, person, context and time-focused was applied in an ethical environment and context. Special attention was paid to the way the patients perceived and experienced the situation. The self-reports of the children and adolescents, concerning the resilience, seemed the most reliable source for registering the protective resources and the quality of life.

We have explored the relationship between value-based practice and evidence-based practice developing a working therapeutic alliance which optimizes the clinical outcomes and quality of life.

That implies that children who have high genetic liability and continue to experience an adverse environment are especially at risk for later maladjustment and professional support is needed.

Assessing genetic and environmental factors, in an ethical, person- and value-centered way, is likely to lead to improvement in the ability to design effective supportive and empowering treatments for children and their families. The fact that the resilience of high-risk and UHR children improved in time after targeted interventions, gives hope that the outcome and the onset of psychosis can be influenced.

Generally, as a future perspective, the prevention and intervention programs should rely on psycho-educational projects as well. These initiatives aim to develop children’s and parents competences and empowerment. The exposure to parent’s symptoms or poor environmental factors is an influential risk factor and the extensive
psychosocial interventions are considered to enhance the protective factors and the quality of life [44].

In our research, the main focus of the interventions was to act ethically, to do no harm and through enhancing the communication skills of the patients; we helped in the acquisition of better strategies to cope with at risk situations. The interventions were phase-specific depending on the specific needs of the patients and their families.

Extensive psychosocial interventions: crisis intervention, assistance in maintaining social functioning, cognitive-behavioral therapy and family therapy have been offered and they proved to be superior to the simple clinical monitoring, regarding the prevention of psychosis in people at ultra-high risk.

The rate of conversion to psychosis of individuals with genetic risk for psychosis is 20%-25%, after 1-2 years according to some existing studies [27]. In our research, after 3 years, only 10% of the genetically high-risk patients converted to psychosis, because they received targeted intervention, adapted to their existent symptoms and psychopathology. This is significant, because children and adolescents are under permanent psychological, cognitive development and it is essential to prevent or to postpone the psychopathologic picture of psychosis.

For those who meet the UHR criteria, the rate of conversion to psychosis, described in literature, is approximately 40-60% depending on time [26, 27]. In our research, even after 3 years, the conversion rate was 15% in the group with needs-focused treatment (pharmacologic adapted to the existent symptoms and extensive psychosocial intervention), respectively 25% in the group with extensive psychosocial intervention. It is an evidence-based proof that early intervention in an ethical framework can bring positive results and benefits for the UHR category.

There are two potential benefits of the therapeutic intervention for prodromal symptoms: by treating symptoms we can potentially reduce the distress and disability and we may reduce the risk of evolution to a more serious condition, such as acute psychosis [27]. Through the development of valid and reliable operationalization criteria for the psychosis risk syndrome, the UHR patients may be one step closer towards determining which interventions are crucial and influential in preserving their good mental health and in maintaining an ethical setting.

Our research-action model of systemic, family-centered evaluation and intervention, proved to be a successful way to enhance the empowerment, the positive aspects of the individual and family functioning. Throughout the research, the needs of the parents as well as of the children were approached simultaneously by creating an interface between the mental health services for children and the adult services, between genetics and gen-ethics, psychiatry and bioethics.

Conclusions

The ethically conducted research on UHR populations provides a significant opportunity to develop a systematic scientific strategy for the early intervention and possible prevention of psychosis.

In designing the prevention or treatment interventions, the selection
of targeted modifiable factors, like resilience and quality of life, would increase the likelihood of a good outcome and healthy adaptation.

The early intervention in an ethical framework might be of top importance in protecting the children’s development, so that the timely attention and early intervention may prevent the course and improve the overall prognosis. It is important to remember that, given the genetic or biological vulnerability, some early intervention strategies applied in an ethical, non-harmful frame, could prevent the onset of psychosis in children and adolescents.

Among the more complex youth mental health cases it may be highly unethical not to intervene and possibly neglect the high needs of this vulnerable group, but the intervention should begin with the most benign treatment administered as early as possible in the illness.

The scientific accuracy, the evidence-based information and ethics of how we use the predictive information requires great attention in constructing an optimistic perspective for the future.

As a consequence of the research based on ethical principles, the standards, values and ethics of the health policies, especially those concerning the mental health can be further improved.

Further services of early detection and intervention in children and adolescents with at risk mental states should be developed, in order to engage and manage young people at risk of developing psychosis in an ethical framework.

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