ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

The prognostic and clinical significance of neuroimagistic and neurobiological vulnerability markers in correlation with the molecular pharmacogenetic testing in psychoses and ultra high-risk categories

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Abstract

We approach an integrated, multidisciplinary, innovative research-action model in children and adolescents with psychosis and ultra high-risk categories. Our main focus was: to investigate the prognostic and clinical significance of neuroimagistic and neurobiological vulnerability markers in correlation with the molecular pharmacogenetic testing in psychoses and ultra high-risk categories; the dynamic evaluation of the clinical evolution for the studied groups in correlation with specific neurobiological and neuroimagistic variables and markers. Our research was conducted in the period 2009–2015 on 87 patients, children and adolescents with psychosis (42 took treatment after pharmacogenetic testing, 45 without) and 65 children with ultra high-risk (UHR) for psychosis – 32 benefited of pharmacotherapy after pharmacogenetic testing and 33 without. Also, the patients were evaluated through magnetic resonance (MR) spectroscopy at baseline and after pharmacotherapy. The efficacy of the chosen therapy in correlation with the pharmacogenetic testing was evaluated through the mean change in the Positive and Negative Syndrome Scale (PANSS) total scores, in the Clinical Global Impression of Severity and Improvement (CGI-S/I), Children's Global Assessment Scale (CGAS) and through the change registered for the relevant neurobiological markers and MR spectroscopy metabolites, from baseline until endpoint in different timepoints. Our results, showed statistically significant differences of the clinical scores between the studied groups. Our research was a proof, sustaining the use of the pharmacogenetic testing in clinical practice and the value of investigating relevant neurobiological and neuroimagistic markers for a personalized, tailored therapy for psychotic patients and neuro-psychiatric UHR categories, as a fruitful pathway of intervention and care.

Keywords: ultra high-risk, pharmacogenetic testing, MR spectroscopy, neuroimagistic markers.

Introduction

Nowadays, a modern approach in the management and follow-up of psychoses implies a multidisciplinary view and imposes integrative correlations between the clinical, neurobiological, neuroimagistic, molecular, pharmacogenetic markers [1–6]. Also, in the frame of mental health, through early detection and intervention strategies, the main focus should be on ultra high-risk for psychosis categories [7–9].

The new perspectives in the field of neuroimagistics and pharmacogenetics give us the opportunity to make some connections between the clinical features, neuronal circuits, the neurobiological and neuroimagistic markers and the further clinical evolution and prognostic in psychoses but also for ultra high-risk for psychosis categories [10–16].

When promoting early detection, preventive strategies, it is important, first of all, to identify some neurobiological, neuroimagistic vulnerability markers, so that we know, in timely manner, which treatment strategy in function of the timepoint and the stage of the psychotic disorder, should be applied [2, 4–8].

This approach implies, not just selective but also indicative prevention for ultra high-risk (UHR) categories, focusing on persons with high risk, who present clinical sub-threshold symptoms, functional decline and positive family history for psychosis, meaning genetic risks. Through this manner, the possibility of prevention of psychotic symptoms and onset is much higher [17–19].

In the modern staging model of UHR and psychosis, the UHR category shows: moderate but under clinical psychotic symptoms, neurocognitive dysfunctions and functional decline [GAF (Global Assessment of Functioning) Scale <70] and neuroimagistic cerebral modifications, changes [MRI (magnetic resonance imaging), MR spectroscopy] [7, 8, 17, 18].

Considering these neuroimagistic vulnerability markers helps us to engage the proper treatment strategy correlated with the clinical psychosis or prepsychotic prodromal stage [7]. Also, these neuroimagistic markers are helpful in quantifying the medication response, the clinical

evolution and they also could have prognostic significance concerning the remission and relapses in psychoses. The UHR category represents a high risk for the psychosis onset and we need to pay special attention that the dysfunctional pattern and low functioning and cognitive decline are also correlated with subsequent neurobiological, neurometabolic processes and pathways [17, 20–26].

The treatment of election in the management of psychosis should be chosen in correlation with the neurobiological, pharmacogenetic, neuroimagistic and clinical profile of the target patients and UHR categories. When choosing the suitable pharmacotherapy, the pharmacogenetic markers should be analyzed carefully, because through the pharmacogenetic testing, the effects of the genetic variations – polymorphisms on the medication response, safety, tolerability and efficacy – are investigated [1, 3, 27–30].

In our present research, we will capture the prognostic and clinical significance of modern pharmacologic treatment approaches, correlated with the evaluation of the neuroimagistic markers, especially through MR spectroscopy and also functional MRI [4, 14, 16, 18, 25]. The main objectives of our study were: the evaluation of the prognostic significance of specific vulnerability markers in the psychosis onset, through the observed differences between the psychosis converters and non-converters from the UHR categories; the efficacy of the different pharmacologic interventions in the child and adolescent psychoses and in the UHR for psychosis group; also, the evaluation, through neuroimagistics – MR spectroscopy and fMRI (functional magnetic resonance imaging) – of the modification of the metabolites/activation of different pathways in correlation with the chosen pharmacotherapy, after and without pharmacogenetic testing [1, 14, 27].

Patients, Materials and Methods

The present research was performed between the years 2009 and 2015, in the University Hospital for Child and Adolescent Psychiatry and Neurology, Timişoara, Romania. We recruited patients, children and adolescents with psychosis but also ultra high-risk categories, who were prone to develop psychosis.

Our actual study is focusing especially on neurobiological, neuroimagistic, respectively clinical aspects and on specific pharmacogenetic correlations.

The diagnoses of the studied patients were put according to DSM IV (Diagnostic and Statistical Manual) and reconfirmed by a child and adolescent psychiatrist through the K-SADS-PL (Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime version) application.

The study samples consisted of 87 patients, children and adolescents with psychosis and 65 patients with UHR of developing psychosis. The patients included in the study were aged between 12 and 20 years (median age 15.78±4 years).

We obtained for each patient the informed assent and the informed consent from the parents/legal guardians. Our study was done in accordance with the Ethical Committee regulations of the "Victor Babeş" University of Medicine and Pharmacy, Timişoara, with the ICH–GCP (International Conference on Harmonization–Good Clinical Practice) regulations and guidelines.

Our study samples were each one divided in two groups: from the 87 children with psychosis – 42 took treatment after pharmacogenetics testing and 45 without the pharmacogenetic testing before the treatment election; from the 65 UHR for psychosis group – 32 took treatment after the pharmacogenetics testing and 33 without.

Clinical evaluation of the patients

In order to analyze the clinical evolution of the patients in each group, we applied the following instruments and scales: PANSS (Positive and Negative Syndrome Scale), CGI-S/I (Clinical Global Impression of Severity and Improvement), CGAS (Children's Global Assessment Scale). PANSS was applied by an authorized rater, in order to offer an objective measure for the psychiatric symptoms, to evaluate the psychopathology, the positive, negative and general symptoms. In order to quantify the presence of adverse events in correlation with the administered antipsychotic medication, we applied UKU (Udvalg for Kliniske Undersogelser) – the adverse events scale, respectively the extrapyramidal syndromes / side effects scales – SAS (Simpson–Angus Scale), AIMS (Abnormal Involuntary Movement Scale), BARS (Barnes Akathisia Rating Scale).

Pharmacogenetic testing

The pharmacogenetic testing was done through the genotyping – SNPs (single nucleotide polymorphisms), through RT-PCR (reverse transcription-polymerase chain reaction), after the DNA prelevation. The genotypes of the allelic variants CYP * have been determined through the specific allelic fluorescence measurement, using the software for allelic discrimination. The identification of the alleles CYP2D6 *3, *4, *5, *41, responsible for the medication metabolizing types, was significant. Genomic DNA was extracted from EDTA (ethylenediamine-tetraacetic acid) blood using QIAamp DNA Mini Kit (Qiagen, Germany). The CYP2D6 genotyping was performed, so that the laboratory staff was blinded to the patients' data.

CYP2D6 *3, *4, *5, *41 allele identification was performed by using TaqMan® Drug Metabolism Genotyping Assay for Allelic Discrimination CYP2D6* and TaqMan® PCR Master Mix (Applied Biosystems) according to the protocol provided by the producer. Genotypes were determined by measuring allele-specific fluorescence using the software for allelic discrimination (Applied Biosystems).

Neuroimagistic investigations (MR spectroscopy and functional MRI)

For the correlation of clinical data with the cerebral biological changes, we performed the neuroimagistic investigations.

The patients have been evaluated through MR spectroscopy at baseline and after the chosen pharmacotherapy with or without pharmacogenetic testing before. Through the MR spectroscopy, we investigated key aspects of the cerebral function and metabolism. We quantified the following neurometabolites: NAA (N-acetylaspartate), GABA (gamma-aminobutyric acid), Asp (Aspartate),

Cr (creatine), Gln (glutamine), GPC (glycerophosphocholine), PC (phosphocholine), PCr (phosphocreatine), Tau (taurine), N-MDA (N-metyl-D-aspartate), serine, glycine, Cho (choline).

We used the MR spectroscopy software package for the MR spectral quantification, which automatically calculates a matrix of the correlation quotients of the cerebral metabolites.

The efficacy of the chosen therapy in correlation with the pharmacogenetic testing has been evaluated through the modification of the applied clinical scales total scores and through the change registered for the relevant neurobiological markers and neurometabolites, from the initial values until endpoint, in each timepoint. So that, we evaluated the efficacy of the chosen pharmacotherapy in correlation with the pharmacogenetic testing and the variation of the cerebral metabolites, quantified through the MR spectroscopy, through the change of the mean total scores of the scales from baseline until endpoint in different timepoints. In the UHR group, we also correlated the transition to psychosis in function of the type of intervention (with and without prior pharmacogenetic testing) and the neurobiological and neuroimagistic status.

Statistical analysis

All analyses were carried out using SPSS software (version 17.0, Chicago, IL, USA) and Microsoft Excel. For comparing the clinical scales scores (PANSS, CGI-S/I, CGAS, UKU, SAS, AIMS, BARS) and also the MR spectroscopy brain metabolites values at different time points, the Friedman non-parametric test for pair values was used. For comparing the clinical response, evolution between the groups – GI (who benefited of pharmacogenetic testing in choosing the proper medication) = G1 (42 psychotic patients) + G3 (32 UHR patients) and the group GII (without pharmacogenetic testing) = G2 (45 psychotic patients) + G4 (33 UHR patients), the Mann–Whitney non-parametric test was applied. For comparing the mean total clinical scales scores and also the MR spectroscopy brain metabolites values at two different time points and in each two with two different timepoints, Wilcoxon signed rank non-parametric test was used.

Results

We obtained significant results through our present research. We identified for the groups (G1 = 42 patients with psychosis and G3 = 32 UHR for psychosis children), where the pharmacogenetic testing was applied, pharmacogenetic polymorphisms at the level of CYP450 enzymes and so we observed in our studied samples the WT (wild type) or normal type metabolizer, the patients who had SNPs, who need in the clinical practice, the adjustment of the doses of the administered pharmacotherapy, as well as careful choosing of the medication and the WT/SNPs (mixed type), who encounter also some difficulties in this area. Therefore, the pharmacogenetic, CYP testing permitted us to choose the proper medication and also to adjust the medication doses accordingly.

In the groups, where the pharmacogenetic testing was not performed (G2 = 45 patients with psychosis and G4 = 33 UHR patients for psychosis), the medication has been assigned according to the clinical symptoms but not to the personalized, pharmacogenetic profile of the patients.

We obtained interesting results, when comparing the study samples (with and without pharmacogenetic testing), concerning the clinical evolution, captured through the clinical psychiatric scales scores from baseline until endpoint but also concerning the variation of the cerebral metabolites values of the MR spectroscopy, in time.

Through the MR spectroscopy, we found modified values and concentrations of the cerebral metabolites for the group of patients with psychosis but also in the UHR patients group:

- very high: GABA values, especially in the prefrontal cortex, glutamate values especially in the frontal cortex, identifying brain lesions;
- very low NAA and NAAG (N-acetylaspartylglutamate) values (Figures 1 and 2).

We also observed high values for the glutamate/glutamine, lactate/NAA, glutamate/Cr, Cho/Cr, NAA/Cr, and NAA/Cho ratios (Figures 3 and 4).

We also obtained interesting results concerning the MR spectroscopy quantified metabolites and their variation from baseline until endpoint (Figure 5).

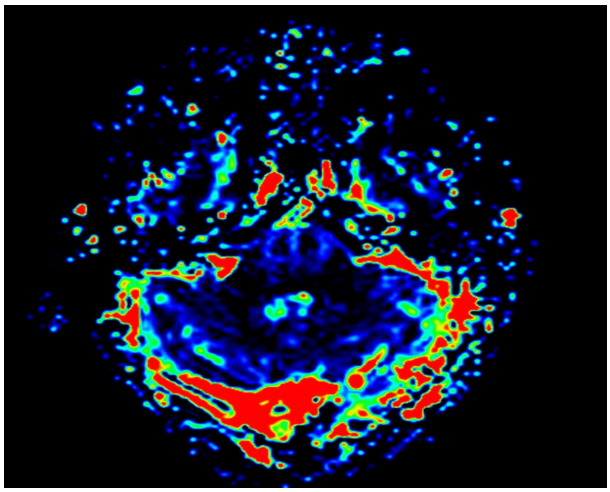

Figure 1 – ***Results for the MR spectroscopy brain metabolites in the psychosis/UHR patient.***

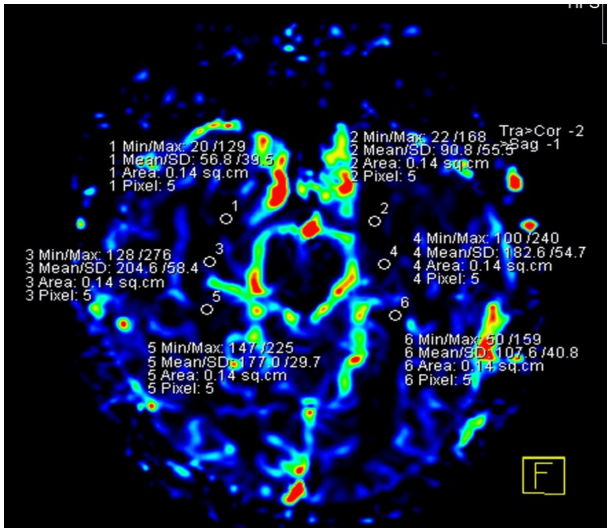

Figure 2 – ***Results for the MR spectroscopy brain metabolites concentrations in the psychosis/UHR for psychosis group.***

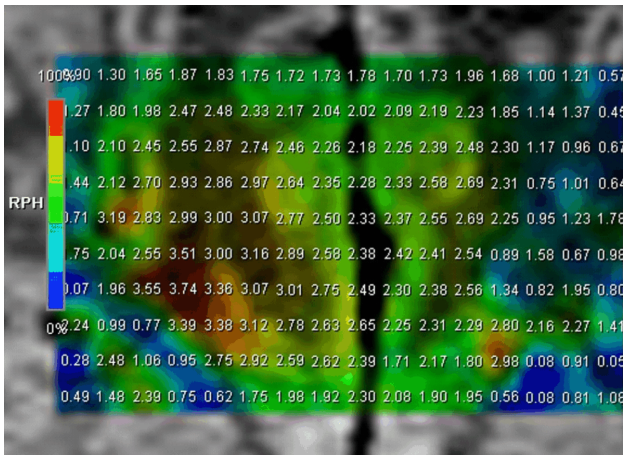

Figure 3 – ***MR spectroscopy matrix quantifying the concentrations of brain metabolites captured. RPH: Relative peak height.***

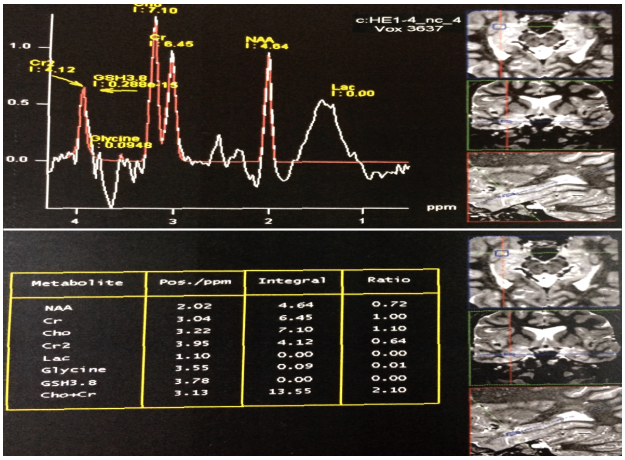

Figure 4 – ***Spectral MR spectroscopy peaks and relevant brain metabolites concentrations/ratios in the studied groups.***

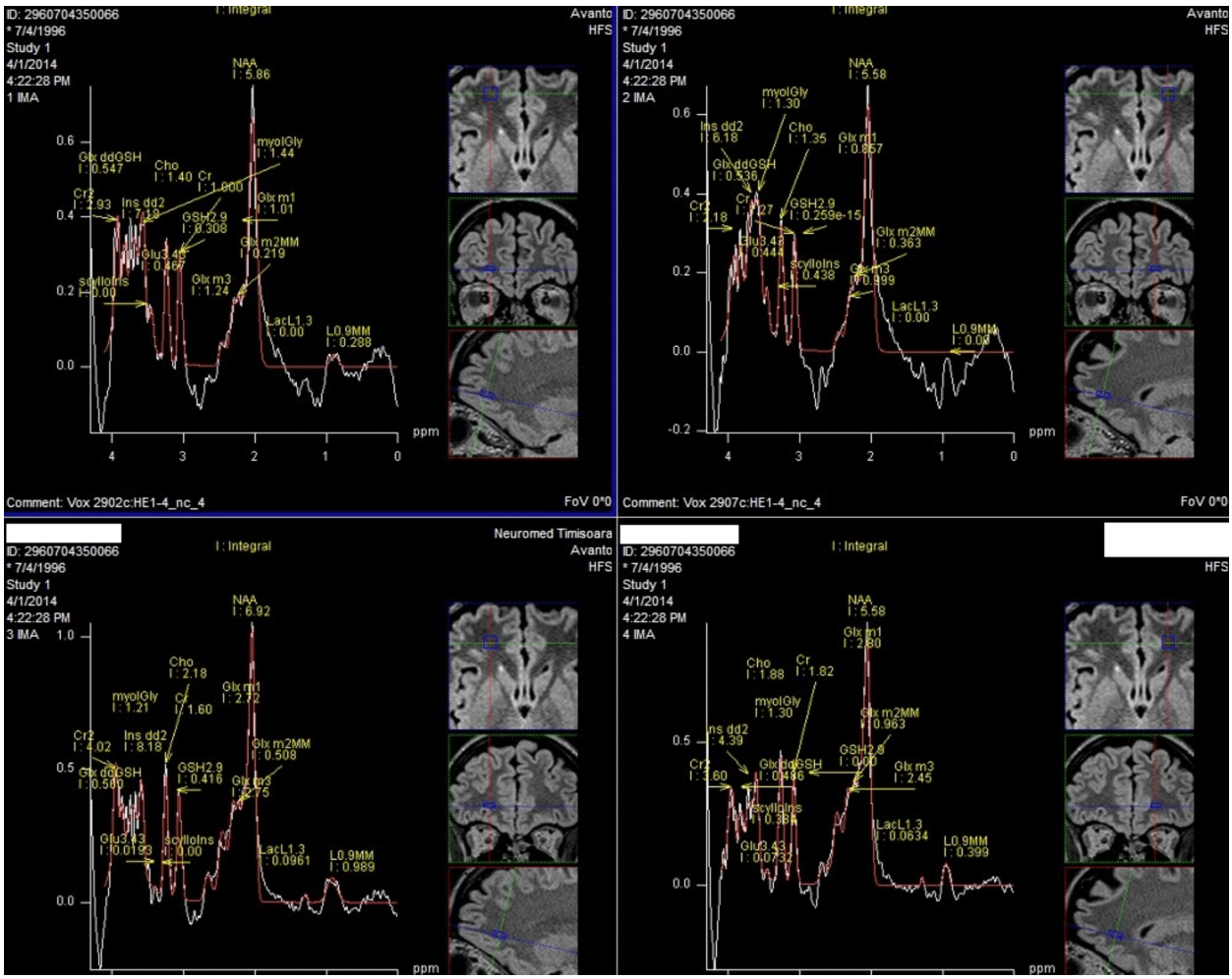

Figure 5 – ***Concentrations, peaks and correlations of MR spectroscopy cerebral metabolites for psychotic and UHR patients.***

So that, we observed the "normalization" of the brain metabolites – the decrease of glutamate and GABA and the increase of NAA and NAAG and the normalization/ decrease of the pathological values of the metabolites' reports after the treatment with correctly chosen medication (antipsychotic, antidepressive, mood stabilizing) in the groups (G1 and G3 = GI), who benefited of prior pharmacogenetic testing.

For the UHR patients for psychosis, the pathological changes of the metabolites were identified even before the onset of psychosis, as vulnerability markers, predicting the transition to psychosis. So that, the pathological changed values of the metabolites before the onset helped us to apply early and targeted pharmacological interventions.

We also made some correlations concerning the neuro-

metabolites' pathways and the treatment response – the patients who had good clinical response, showed also the normalization of the metabolites' levels identified through the MR spectroscopy.

In both study samples (with psychosis and UHR for psychosis), we obtained statistically significant differences of the clinical scales scores, between the patient group, who benefited of pharmacogenetic testing, when choosing the proper pharmacotherapy and the other group, in each timepoint and also between baseline and endpoint values of the evaluation for all the scales (p<0.001, significance level α=0.001). The PANSS and CGI-S scores registered a statistically significant decrease, the CGAS functioning scores showed an improvement and the MR spectroscopy metabolites values improved, implying a good clinical evolution in the pharmacogenetically tested group. We took into account the fact that high PANSS and CGI-S scores mean a poor clinical evolution and decreased scores are correlated with a clinical improvement.

Through comparing the total clinical scale scores (PANSS, CGI-S, CGAS) and the values of the MR spectroscopy brain metabolites in each two with two different timepoints, through the application of the Wilcoxon signed rank non-parametric test, we obtained statistically significant differences for the group – GI, who benefited of pharmacogenetic testing, with choosing the suitable (antipsychotic, antidepressive) medication, proving a good clinical evolution in time (p<0.001, significance level α=0.001).

The obtained results proved that the patients, who took medication chosen after the prior pharmacogenetic testing, registered the improvement of the MR spectroscopy metabolites, as a positive response to the chosen pharmacotherapy.

In the other group – GII, without pharmacogenetic testing, we could observe clinical poor or non-response, lack of improvement of the MR spectroscopy captured brain metabolites correlated with multiple adverse effects in the UKU scale and/or with extrapyramidal symptoms registered through the SAS, AIMS, BARS scales.

Comparing the differences between the two analyzed groups (GI and GII), concerning the total mean clinical scales scores (PANSS, CGI-S, CGAS) for each analyzed moment, applying the Mann–Whitney non-parametric test, we observed the decrease of the PANSS and CGI-S scores and increased CGAS scores, meaning good clinical evolution in the GI group (with pharmacogenetic testing) and poor clinical evolution with non-response in GII (without pharmacogenetic testing).

Through applying the Pearson test, we obtained as correlations' results, both in the psychotic patients group (G1 – with pharmacogenetic testing) and in the UHR group (G3 – with pharmacogenetic testing), the following statistical significant positive correlations between the improvement of the brain metabolites' values in MR spectroscopy and the pharmacogenetic testing application for choosing the suitable pharmacotherapy, and the good clinical response and evolution captured through the improvement of the clinical psychiatric scales scores (Table 1).

Table 1 – ***Spearman's correlations transformed z, between the psychiatric clinical scale scores and the MR spectroscopy metabolites improvement for the studied groups***

Correlations	Patients with psychosis						UHR for psychosis					
	G1 with pharmacogenetic testing			*G2 without pharmacogenetic testing*			*G3 with pharmacogenetic testing*			*G4 without pharmacogenetic testing*		
	*r**	*z***	*z-STD***	*r**	*z***	*z-STD***	*r**	*z***	*z-STD***	*r**	*z***	*z-STD***
Lower total PANSS scores – Metabolite values improvement	.989	**.511**	**.377**	**.318**	**.359**	**.383**	.974	**.856**	**.699**	**.264**	**.186**	**.932**
Lower CGI-S scores – Metabolite values improvement	.997	**.345**	**.305**	**.221**	**.321**	**.263**	.982	**.189**	**.185**	**.119**	**.235**	**.177**
High functioning CGAS scores – Metabolite values improvement	.985	**.841**	**.679**	**.653**	**.711**	**.709**	.989	**.621**	**.564**	**.387**	**.358**	**.354**

MR: Magnetic resonance; UHR: Ultra high-risk; PANSS: Positive and Negative Syndrome Scale; CGI-S: Clinical Global Impression of Severity; CGAS: Children's Global Assessment Scale; *r*: Spearman's correlation; *z*: Transformed value; STD: Standard deviation; *: Coefficient of determination; **: Coefficient of non-determination.

Also, in the UHR group, we obtained statistical significant results concerning the rate of transition to psychosis in correlation with the applied intervention type – with or without pharmacogenetic testing prior to choosing the proper medication. The psychosis transition rate was much higher, 35.7% for the group without pharmacogenetic testing and 3.7% in the group with pharmacogenetic testing.

In the UHR group, we found the best positive correlations, with highest psychosis transition rates for those patients who showed pregnant vulnerability markers (early neurobiological, neuroimagistic modifications), captured through the neuroimagistic investigations (MR spectroscopy and fMRI).

Through fMRI, we captured some relevant vulnerability markers, expressed through the altered, dysfunctional brain activation pathways, in both groups: for the psychotic patients but also for the majority of UHR patients.

Combining the functional imaging with cognitive tasks – n-back and emotional re-appraisal, in order to investigate the functions, as well as the connectivity of the brain networks, we obtained valuable results.

Through the n-back task – test of the working memory, we observed for the psychotic/UHR patients in comparison with the normal healthy controls:

- a weaker activation of the right prefrontal area (Figure 6, a and b);

▪ a weaker activation of the median dorsal prefrontal area and higher activation of the dorsal and rostral anterior cingulate, which is implied in the emotional processing of the anxiety type (Figure 6, c and d);

▪ a weaker activation, mainly in the frontal and prefrontal areas, mainly in the left hemisphere, meaning low concentration abilities (Figure 6, e and f);

▪ so, we observed the high mobilization of the brain area implied in emotional and stress processing, of obsessional and rumination type with the dysfunction of the cognitive and attentional processes;

▪ so, we were able to identify some relevant vulnerability markers.

Through the fMRI emotional re-appraisal task, we evaluated the capacity of the patients to control their negative affects. Knowing the fact that the performance on this task lays in the activation of the lateral and dorsal prefrontal areas, so that high activation means a good ability to stop the negative information processing, we observed for the psychotic and UHR patients: low activation of these areas, correlated with the incapacity to stop the reinterpretation of negative emotions.

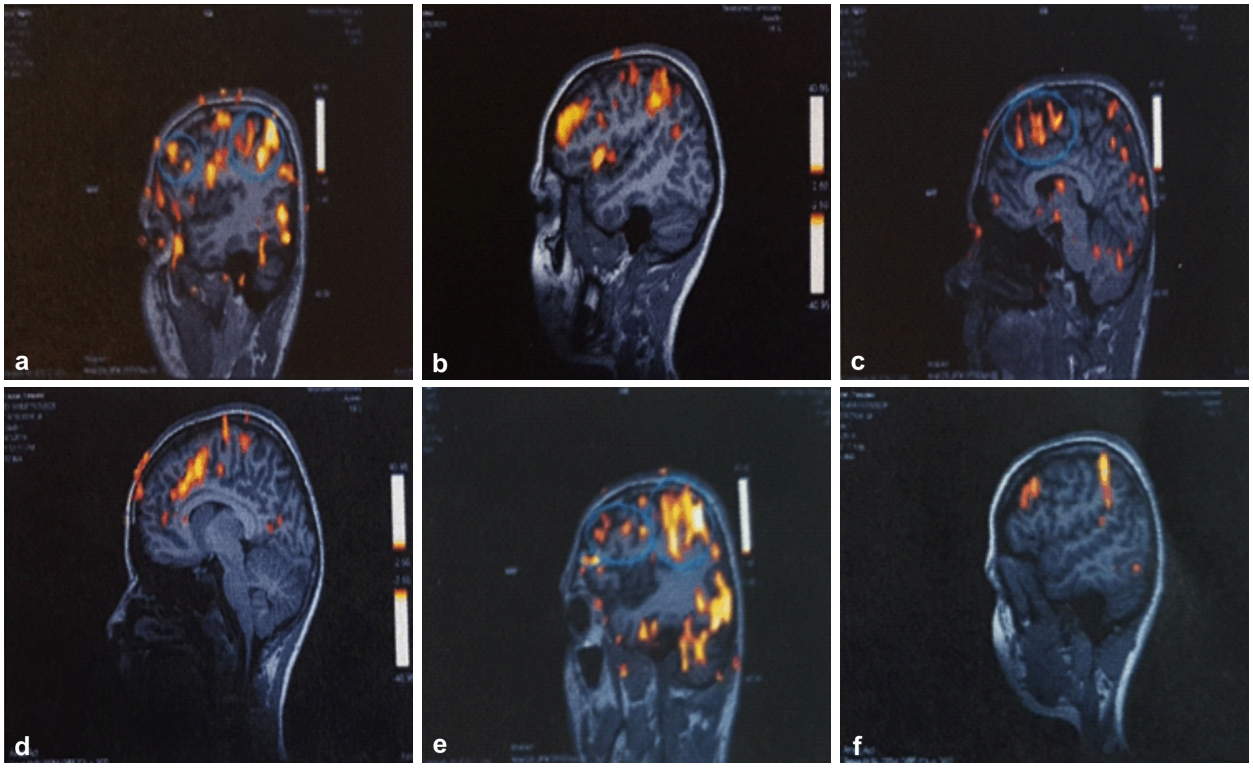

Figure 6 – ***(a) fMRI n-back task and emotional re-appraisal task with high activation of the right prefrontal area in normal healthy controls; (b) fMRI n-back task and emotional re-appraisal task for psychotic/UHR patients with weak activation of the right prefrontal area; (c) fMRI n-back task and emotional re-appraisal task – sagittal incidence with high activation of the median dorsal prefrontal area and low activation of the dorsal and rostral anterior cingulate in normal healthy controls; (d) fMRI n-back task and emotional re-appraisal task – sagittal incidence with weak activation of the median dorsal prefrontal area and high activation of the dorsal and rostral anterior cingulate in psychotic/ UHR patients; (e) fMRI n-back task and emotional re-appraisal task – with high activation of the frontal area, mainly in the left hemisphere, in normal healthy controls; (f) fMRI n-back task and emotional re-appraisal task – with weak activation of the frontal area, mainly in the left hemisphere, in psychotic/UHR patients.***

Discussion

In the actual general context, our present research, offers new perspectives, especially because of the lack of consistent studies for children and adolescents with psychosis and with ultra high-risk, concerning the modern molecular, pharmacogenetic testing correlated with modern neuroimagistic investigations and up to date clinical psychiatric scales. Some of the pharmacogenetic and neuroimagistic aspects have been approached in some studies in adults but there is a lack of research concerning the pediatric population. The pharmacogenetic studies in general in Romanian population are rare.

Our study is especially valuable in the light of a multidisciplinary approach, implying complex correlations between the clinical, neurobiological, pharmacogenetic and neuroimagistic markers [1, 2, 4–6].

Our present research opens the perspective of the personalized pharmacotherapy for children and adolescents, which is tailored to the genetic variability, the neuroimagistic and neurobiological particularities. Therefore, the MR spectroscopy permitted us the *in vivo* identification and quantification of the biochemical substances and neurometabolites [4, 17, 31, 32]. Also, the goal of the fMRI data analysis was to detect correlations between brain activation and a task the subject performs during the scan and helped us discover correlations with the specific cognitive states, such as memory and recognition, induced in the analyzed subject [33–40].

Our obtained results of the present study are in line with some in the adult population existing researches concerning pharmacogenetic testing and the neuroimagistic modifications of the brain metabolites in psychosis and UHR categories but as far as we know, there is a lack of

information about the integrative correlations of the variables and markers [7, 9, 12, 14, 15, 18, 41, 42]. Also, in the pediatric population, there is a lack of information and studies in this area of research.

Concerning our obtained results, the fact that we observed, also in the UHR for psychosis patients, the same neuroimagistic brain metabolites' modifications like in psychosis, was a big step forward.

This fact is relevant in order to apply targeted early detection and intervention strategies for UHR categories, in an ethical frame [8]. Detecting the neuroimagistic and clinical vulnerability markers could help the clinician to make a timely difference between the psychosis converters and non-converters [9].

It is also significant that our obtained results proved the fact that some relevant vulnerability markers, captured early, were in high positive correlation with the further clinical evolution of the patients, proving a high prognostic and predictive value.

For the UHR patients for psychosis, the pathological changes of the metabolites could be identified as vulnerability markers, even before the onset of psychosis. So that, the identification of the modifications of the brain metabolites specific for psychosis, captured through the MR spectroscopy, can help us to apply early detection and intervention strategies for the UHR for psychosis patients. Through the modern neuroimagistic investigations, we can detect the neurometabolic modifications before the clinical prodrome of psychosis and we can apply targeted interventions in order to postpone and even prevent the onset of psychosis. Some of the modifications and pathological values of the brain metabolites are reversible and can be corrected through the proper neuropsychopharmacological interventions applied [14, 15, 19].

Also, for the patients with already installed psychosis, some of the cerebral metabolites' modifications are reversible, if proper, carefully chosen pharmacotherapy, in function of the pharmacogenetic, neuroimagistic and clinical profile of the patient, is administered.

Analyzing the modifications captured for the psychotic and UHR categories, through the MR spectroscopy, we observed some relevant aspects, some of them being in line with the existing literature [2, 9, 31, 32] and some not [19].

Recent work has questioned the prognostic significance of non-transition/transition markers in UHR patients [7, 9]. It is difficult to predict outcomes at an individual and generalized level, based on the clinical features and the neuroimaging investigations may be able to help improving prediction [2, 7, 31, 32].

Approximately 35% of UHR will go on to further be diagnosed with psychosis, usually within 24 months [2, 9]. That is why there is a pressing need to identify relevant biomarkers that can detect those UHR subjects, who are most likely to develop psychosis [36].

The most relevant vulnerability markers in psychosis were: NAA, NAAG, GABA and glutamate [41, 42].

The NAA, which has a neurotrophic role, was very low for the psychotic and UHR patients. On this fact relies the value of some antidepressive treatments, which have a neuroprotective, neurotrophic role, because they prevent the decrease of NAA in the brain [4].

The glutamate, being a brain metabolite with significant role in the neurotransmission, has very high values in psychotic, UHR patients but also for the UHR patients, offspring of psychotic parents. The glutamatergic pathways are implied in the cognition and memory processes and the excessive concentrations of glutamate in the brain are neurotoxic. On this principle relies the efficacy of some antidepressive treatments and of the lithium, as neurostabilizers, which decrease the brain glutamate values [4, 14, 18].

The observed low values for NAA and NAAG in the frontal and temporal lobe, in the thalamus, these metabolites representing neuronal integrity markers, with relevant roles in mediating and modulating the superior mental functions, are in line with the data obtained by Brugger *et al.* (2011), also concerning disorders like multiple sclerosis and Alzheimer [17].

Some of the neurometabolic, neurochemical, neurobiological, neuroimagistic modifications persisted even after the clinical remission of the psychotic patients, as significant vulnerability markers and scar of the past psychotic episodes. The psychoses reflect disruptions in the functions of extended brain networks.

The management of the UHR categories and of the prodromal psychotic states remains a challenge for the clinicians and psychiatrists, because of the complex ethical implications [8]. Therefore, the case management will be individualized and adapted to the particular needs of every patient.

Further research is needed in the field of child psychiatry/psychiatry, pharmacogenetics and neuroimagistics, in order to develop a genetically informed, personalized medicine, although some promising researches concerning the genetic liability, the vulnerability markers and their clinical application, have already been done.

Through targeted interventional strategies, the clinical evolution and prognosis of psychotic and UHR patients can be improved.

This represents a valuable future perspective in the clinical practice, because a personalized therapy adapted in function of the genetic, pharmacogenetic, neurobiological, spectroscopic profile, could be chosen as first line indication. The results of our research and clinical practice plead for the utility of this modern integrative approach in child psychosis.

Conclusions

The pharmacogenetic testing, the fingerprinting of the neurobiological and spectroscopic, MR spectroscopy markers, represent strongly predictive factors of the clinical evolution in child psychoses and UHR categories, also after the administration of psychiatric medication. The pharmacogenetic testing proved to be a significant predictor for the clinical evolution of the psychotic and UHR patients and of the response to pharmacotherapy. The evaluation of neurobiological and neuroimagistic markers in psychotic patients and UHR categories, proved the high clinical utility in prevention, early detection and intervention in psychiatry. Therefore, the modifications of the brain metabolites become a dynamic measure of the vulnerability mechanisms in child psychoses and ultra high-risk categories. Our research was a proof that

sustains the implementation of the pharmacogenetic testing and the value of investigating the relevant neurobiological and neuroimagistic markers, in the clinical practice, for a personalized, individualized therapy in child psychoses and for UHR categories, as a fruitful path of care and intervention.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

This research was done in the Center of Genomic Medicine from the "Victor Babeş" University of Medicine and Pharmacy, Timişoara, POSCCE Project ID: 1854, cod SMIS: 48749, "Center of Genomic Medicine v2", contract 677/09.04.2015.

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Received: June 26, 2015

Accepted: November 21, 2016