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The effect of neurobiological changes in the brain of children with schizophrenia, ultra high-risk for psychosis and epilepsy: clinical correlations with EEG and neuroimagistic abnormalities

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Abstract

Relatively little research has been conducted on quantitative electroencephalography (QEEG) activity in patients with psychosis/schizophrenia, especially in populations at-risk for the illness. Further studies are needed, in order to offer a possible endophenotypic marker of the cerebral functioning, associated with psychosis/schizophrenia, in correlation with the neuroimaging, the neurocognitive, biochemical, molecular genetic tests, clinical aspects and the EEG activity from the same subjects. The aim was to investigate the role the QEEG abnormalities play in the etiology of psychosis/schizophrenia, whether it can provide an endophenotype for psychosis and to make some correlations with the results obtained through magnetic resonance (MR) spectroscopy, for proper early detection and intervention. The prospective research was performed in the University Clinic of Child and Adolescent Psychiatry, Timişoara, Romania, involving 55 children with schizophrenia or ultra high-risk (UHR) for psychosis (groups 1, 2, 3 and 4) and 55 children as healthy controls (group 5). Groups 1 and 2 (28 children) are diagnosed with schizophrenia, groups 3 and 4 are UHR for psychosis (27 children), and group 5 represents healthy controls. Groups 1 and 3 had convulsive seizures in their personal history. We noticed: through the QEEG, numerous patterns of theta and delta activity, the diminished amplitude of the alpha band waves and the diminished alpha activity; also, the onset of psychosis was earlier at those presenting convulsive seizures in their personal history (groups 1 and 3); also, specific neuroimagistic abnormalities and modifications. The cerebral lesions, appearing during the development, raise the liability for schizophrenia. The high-risk for schizophrenia is correlated with the personal history of epilepsy, as well as with the family risk for psychosis.

Keywords: schizophrenia, psychosis, neurobiological, EEG abnormalities, neuroimagistic, ultra high-risk.

Introduction

Schizophrenia is a clinically heterogeneous disorder and given the imperfection of current psychiatric diagnostic systems to capture this heterogeneity, family-based high-risk studies should be further done [1–5].

According to the neurodevelopmental model of schizophrenia, early pre- or perinatal insults may interfere with normal brain development and entail subtle brain abnormalities [1, 2].

Increasing research attention was given to the role of cognitive development, neurobiological correlates, including biochemical and electroencephalography (EEG) studies. According to the neurodevelopmental model of schizophrenia, the biological onset occurs during fetal neurodevelopment [6–8].

The "soft" neurological signs may be a childhood manifestation of a genetic susceptibility to schizophrenia. "High-risk" studies (offspring of schizophrenic parents) revealed an increased incidence of neurosensory and neuromotor deficits in the children of schizophrenic mothers [3]. These neurobehavioral impairments may

be early manifestations of the brain lesions [9]. The psychotic symptoms emerge as a manifestation of specific neurobiological dysfunctions. It is significant to study the ultra high-risk (UHR) populations. The investigation of the vulnerability markers in the high-risk population is of high interest, because it can bring informations concerning the biological and environmental causes of psychoses [3].

The electroencephalogram (EEG) recorded from the human scalp is widely used to study cognitive and brain functions in schizophrenia. The EEG provides a powerful noninvasive tool for studying the brain mechanisms of attention and information processing in health and disease. Due to its high temporal resolution, the EEG is ideally suited to examine the rapidly changing patterns of brain activities that underline human cognitive function and dysfunction. The scalp EEG is believed to reflect mainly the summated postsynaptic potentials from large synchronously activated populations of pyramidal cells in the cerebral cortex [10–12].

The recorded EEG activities show changes over time, which are often rhythmic or oscillatory in the sense that they alternate regularly. The rhythmic activities in the resting or "spontaneous" EEG are usually divided into several frequency bands (delta: <4 Hz, theta: 4–8 Hz, alpha: 8–12 Hz, beta: 12–30 Hz, and gamma: 30–70 Hz or higher, centered at 40 Hz), which are associated with different behavioral states, ranging from sleep and drowsiness to relaxation and heightened alertness and mental concentration, yet there exists little consensus on the precise frequency limits of each band [13–16]. The EEG has a well-established value and role in the clinical assessment, diagnosis and management of patients with certain neurological disorders, such as sleep disorders and epilepsy [17–19].

The main aims of our study were: to illustrate, that these neurophysiological measures can offer valuable quantitative biological markers of basic pathophysiological mechanisms and cognitive dysfunctions in schizophrenia; that they can be utilized to gain deeper theoretical insights into illness etiology and pathophysiology and may lead to improvements in early detection and more effective and targeted treatment of schizophrenia [14]; to investigate the role, resting QEEG abnormalities play in the etiology of psychosis, and whether it can provide an endophenotype for psychosis; and to make some neuroimagistic correlations, concerning magnetic resonance (MR) spectroscopy abnormalities and modifications [20–22].

The MR spectroscopy is a versatile, non-invasive instrument, which permits the *in vivo* identification and quantification of the biochemical substances and neurometabolites in the brain. It is very useful, for the clinical evaluation and longitudinal monitoring [21, 23].

Patients, Materials and Methods

The prospective research was performed in the University Clinic of Child and Adolescent Psychiatry, Timişoara, Romania, between the years 2010–2017, involving 55 children with schizophrenia or UHR for psychosis (groups 1, 2, 3 and 4) and 55 healthy controls (group 5). Groups 1 and 2 (28 children – 16 girls and 12 boys) are diagnosed with schizophrenia, groups 3 and 4 are UHR for psychosis (27 children – 11 girls and 16 boys), and group 5 represents healthy controls (27 girls and 28 boys). The UHR for psychosis children were also referred to our Clinic because of their existent psychopathology.

Through our research, which offered an ethical frame to our daily clinical practice with children and adolescents with schizophrenia and psychosis risk syndrome, we respected the procedural ethics, a notice of acceptance from the Ethics Committee being obtained. We obtained for each patient less than 18 years, 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 Babeş" University of Medicine and Pharmacy, Timişoara and with the *International Conference on Harmonisation–Good Clinical Practice* (ICH–GCP) regulations and guidelines.

The 11 patients from group 1 are children with schizophrenia, who had before the schizophrenia onset, cerebral seizures–epilepsy in their personal history. The 17 children from the group 2 had other psychopathologic disorders pre-morbidly. Groups 3 and 4 are represented by the UHR children for psychosis. Group 3 is represented by 14 children with a personal history of cerebral seizures. The patients from the group 4 are represented by 13 children with other psychopathologic disorders before the onset of UHR attenuated psychotic symptoms. The group 5, being the healthy control group, is represented by 55 healthy children, 28 boys and 27 girls, who benefited from EEG evaluation. In all study groups, the patients were aged between 9 and 20 years.

This study is focused on the quantitative electroencephalography (QEEG) at rest, where psychiatric patients have shown abnormal patterns of activity compared to healthy controls. Quantitative EEG amplitudes at rest were compared across four frequency bands between the four groups. Our interest was focused on the evaluation of transition of the UHR category to psychosis.

Neuroimagistic investigations (MR spectroscopy)

For the correlation of clinical data with the cerebral biological changes, we performed the neuroimagistic investigations. The patients have been evaluated through MR spectroscopy. Through the MR spectroscopy, we investigated key aspects of the brain function and metabolism.

We quantified the following neurometabolites: *N*-acetyl aspartate (NAA), *γ*-Aminobutyric acid (GABA), Aspartate (Asp), Creatine (Cr), Phosphocreatine (PCr), Glutamine (Gln), Glutamate + Glutamine (Glx), Glycerophosphocholine (GPC), Phosphocholine (PC), Phosphocreatine (PCr), Taurine (Tau), *N*-methyl-D-aspartate (NMDA), Inositol (Ino), Serine, Glycine, Choline (Cho).

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.

Statistical analysis

All analyses were carried out using Statistical Package for the Social Sciences (SPSS) software (version 17.0, Chicago, IL, USA) and Microsoft Excel.

We also applied the Pearson's test for the correlation of the obtained results and Spearman's correlations transformed *z*.

Results

Group 1

Among the 55 children participating in this study, 11 were included in group 1 (four girls and seven boys). The average age of the onset of the first psychotic episode for the girls included in this study was 13.4 years. The onset of schizophrenia was observed around the age of 15 (Figure 1).

The average age of the first psychotic episode for the boys was 14 years, while the average age for the onset of schizophrenia was 15.2 years. The average age for having their first psychotic episode was 13.7 years, while the average age for the onset of schizophrenia was 15.14 years (Figure 2).

Group 2

From the 17 children that were included in group 2, 12 were boys and five were girls. The average age registered for the onset of the first psychotic episode in girls was 15 years, while the onset of schizophrenia occurred at an average age of 16 years. The boys from this group had an average age of onset of the first psychotic episode of 15.6 years, while the average age for the onset of schizophrenia was 17 years. The average age of the children having their first psychotic episode was 15.6 years, while the average age of schizophrenia onset of was 16.5 years. A predominant ratio of boys has been observed in the report of group 1 (boys/girls 7:4), while in group 2, the girls were more predominant (boys/girls 5:12). These results are aligned with the ones from the literature on the subjects, which underlines the predominance of the presence of neurodevelopmental signs in boys. Comparing both the average age of the first psychotic episode (FEP), and the average age of schizophrenia onset for the two groups, a younger age has been observed in both cases in group 1: 13.7 years FEP in group 1, comparing to 15.3 years FEP in group 2, and 15.14 years for schizophrenia for group 1 *versus* 16.5 years for schizophrenia for group 2.

Group 3

This group has been formed by 14 children and adolescents (10 boys and four girls), which registered in their personal history convulsive seizures and developed UHR attenuated psychotic symptoms and decrease in their socio-scholar functioning. A gender-based distribution can be observed in Figures 3 and 4. It can be observed that the average age for the girls is 14.75 years and for the boys is 14.1 years. The average age for the first psychotic symptoms was 14.42 years.

Group 4

Group 4 is represented by 13 UHR children for psychosis, from which seven girls and six boys, who did not had premorbid seizures, which represents the basis of psychosocial functioning. The average age registered in this group was 15.42 years for the girls and 15.33 years for the boys. Comparing the average age of the onset of the psychotic symptoms for the groups 3 and 4, we can observe that the age is lower for the group 3 – 14.42 years (group 4 – 15.37 years). In both groups, registered with convulsive seizures in their personal history (groups 1 and 3), psychotic symptoms appeared earlier than in groups 2 and 4.

Results concerning study groups characteristics

Regarding the positive family history of psychosis, 63% patients of the group 1 and 52% of group 2 had a parent with schizophrenia or bipolar disorder. Meanwhile, 85% patients of group 3 and 23% of group 4 had a positive family history of psychosis. The youngest age of psychosis and schizophrenia onset was registered in patients whose mothers had schizophrenia, especially if the mother's schizophrenia onset has been registered before the birth date of the child or in the first two or three years of the child's life.

EEG results obtained from the study groups

We observed generalized patterns of increased theta and delta activity, a decreased dimension complexity, the result of the overall brain dysfunction (seen especially in group 1), decreased alpha activity and reduced alpha peak frequencies and paradoxical or "forced" EEG normalization (group 3).

Figures 5–8 present the EEG patterns in all the four study groups.

A low voltage appears in 41.81% of cases, with a little increase for the group 2. The beta pattern of EEG has been found in 52.72% of the studied results, registering a higher frequency than in group 2 (18.18%, and 12.72% in group 4). Beta frequencies have been found in 9% of group 2 subjects, appearing predominantly in girls over 16 years. Theta rhythms have been registered in 49.09% of the EEGs, with a higher frequency in group 3 (20%) and in groups 1 and 2 (12.72%). The lowest frequencies of the theta rhythm belonged to group 4 (3.63%) and group 5 (2% of the subjects between 9 and 10 years and 1% of the subjects between 11 and 12 years). Delta rhythms were registered in 25.45% of cases, the higher frequency being observed in group 3 (10.90%), while the lowest one was registered in group 1 (9.09%). 2% of cases were between 9 and 10 years and 1% appeared at the age between 11 and 12. Spikes and waves oscillations have been found in 21.81% of the studied cases, registering the higher frequency in group 3 (90.9%) and the lowest one in group 4 (1.81%).

Among the group 5, patients registering spikes and waves oscillations, 1% were between 9–10 years old and 2% were between 13–14 years old.

The EEG with occipital alpha rhythm has been found in 18.18% of cases with the age between 8–12 years. These results were the most common in group 2 (7.28%) and the most rare in group 3 (3.63%) and group 1 (1.81%). The EEG with occipital alpha rhythm appeared in 37%

of the cases at an age of over 16 years. Monomorphic generalized alpha rhythm appears in our study in 21.81% of cases, from which 12.72% in group 2 and 9.09% in group 4.

In group 5, the monomorphic generalized alpha rhythm appears in 30% of cases. Figure 9a presents the EEG before the normalization, the EEG being done during the period of evolution of generalized tonic-clonic convulsive seizures. The EEG captures generalized paroxysmal hypersynchron discharges of peak-wave complexes. Figure 9b shows the EEG patterns of paradoxical or "forced" EEG normalization (group 3 – UHR for psychosis), the forced normalization of EEG occurring concomitantly with the onset of psychotic disorders.

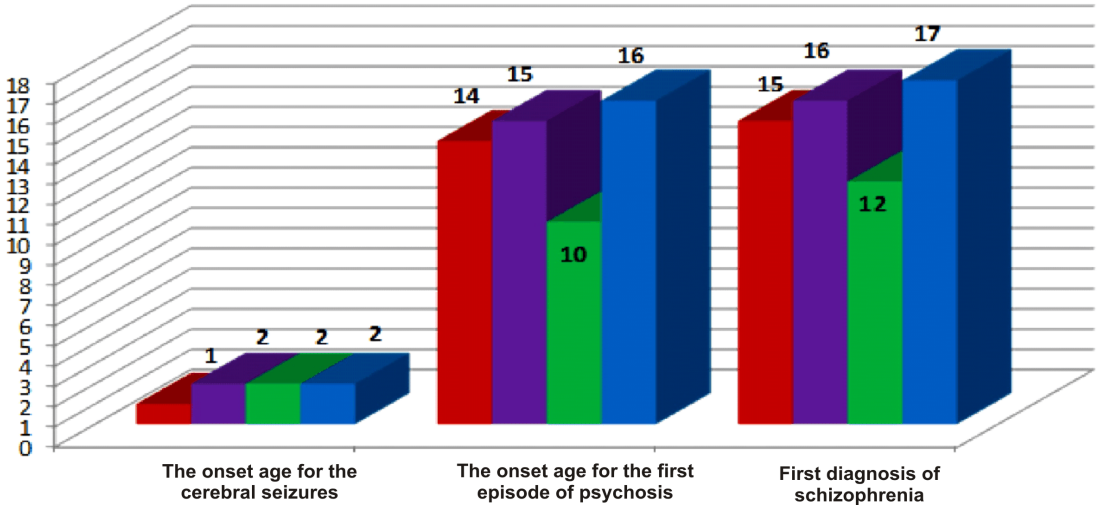

Figure 1 – ***Onset age [years] of cerebral seizures, first episode of psychosis and schizophrenia in the study group 1 – girls.***

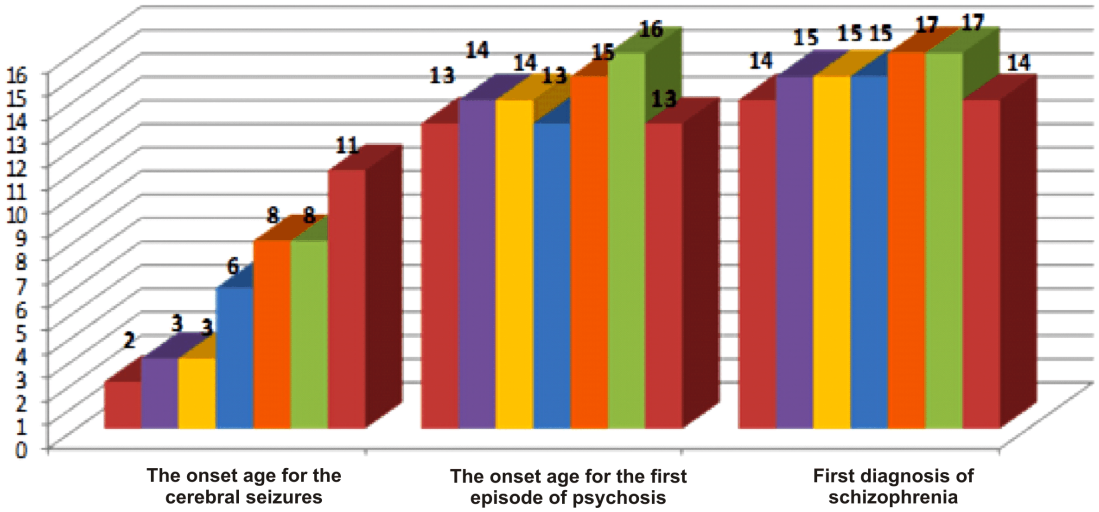

Figure 2 – ***Onset age [years] of cerebral seizures, first episode of psychosis and schizophrenia in the study group 1 – boys.***

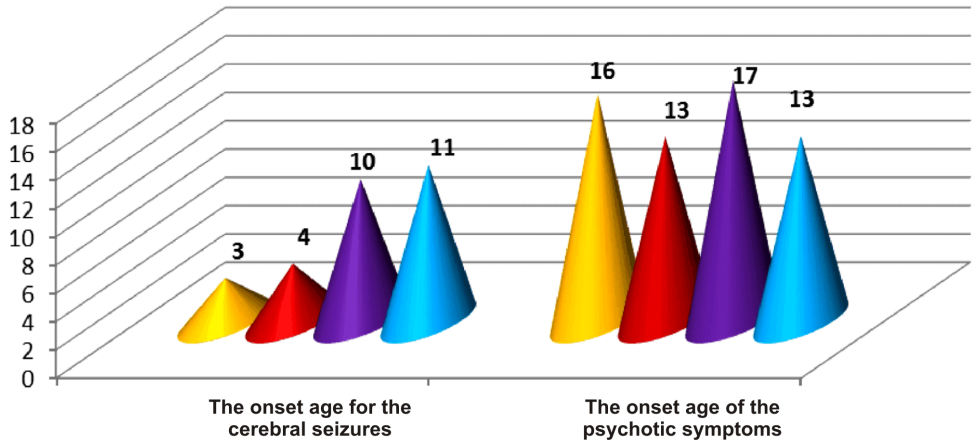

Figure 3 – ***Onset age [years] for the cerebral seizures and of the attenuated psychotic symptoms in the UHR group (study group 3) – girls.***

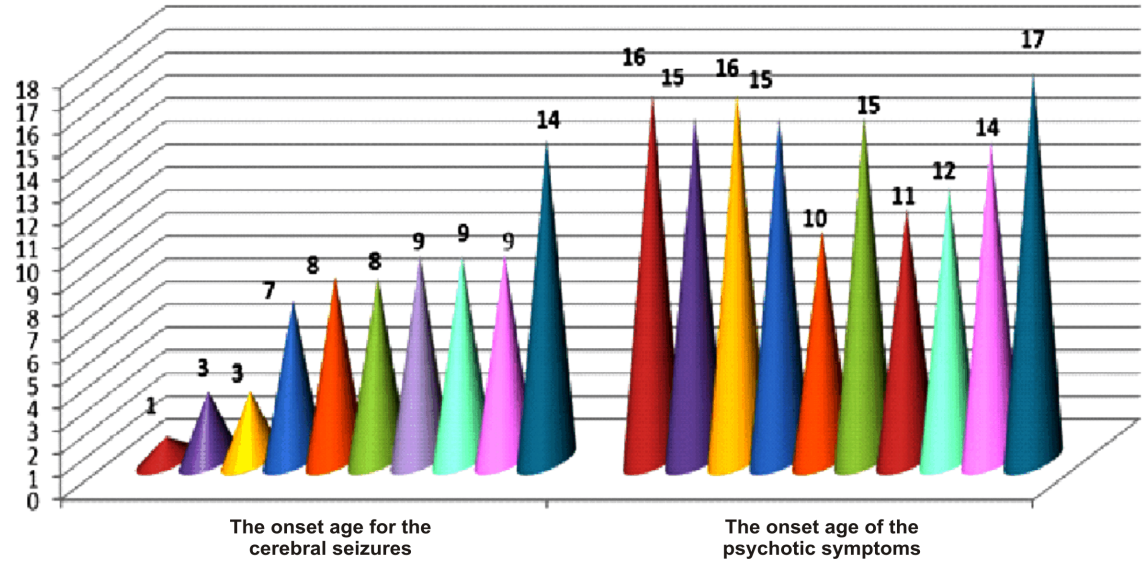

Figure 4 – ***Onset age [years] for the cerebral seizures and of the attenuated psychotic symptoms in the UHR group (study group 3) – boys.***

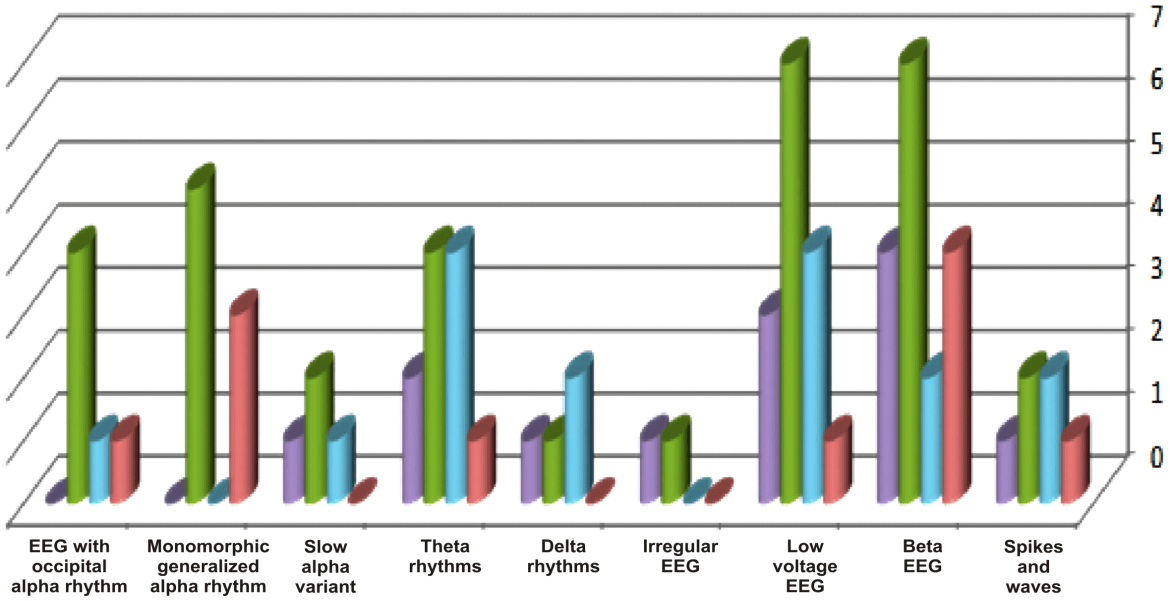

Figure 5 – ***EEG in the study groups (1, 2, 3 and 4), total number of 55 children – for the girls.***

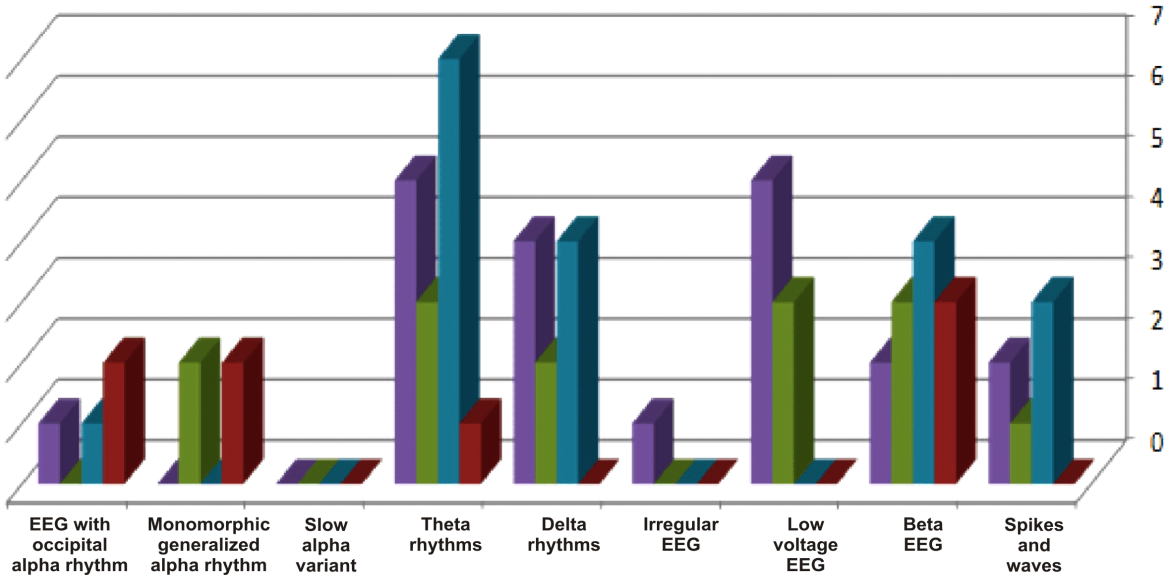

Figure 6 – ***EEG in the four study groups for the boys.***

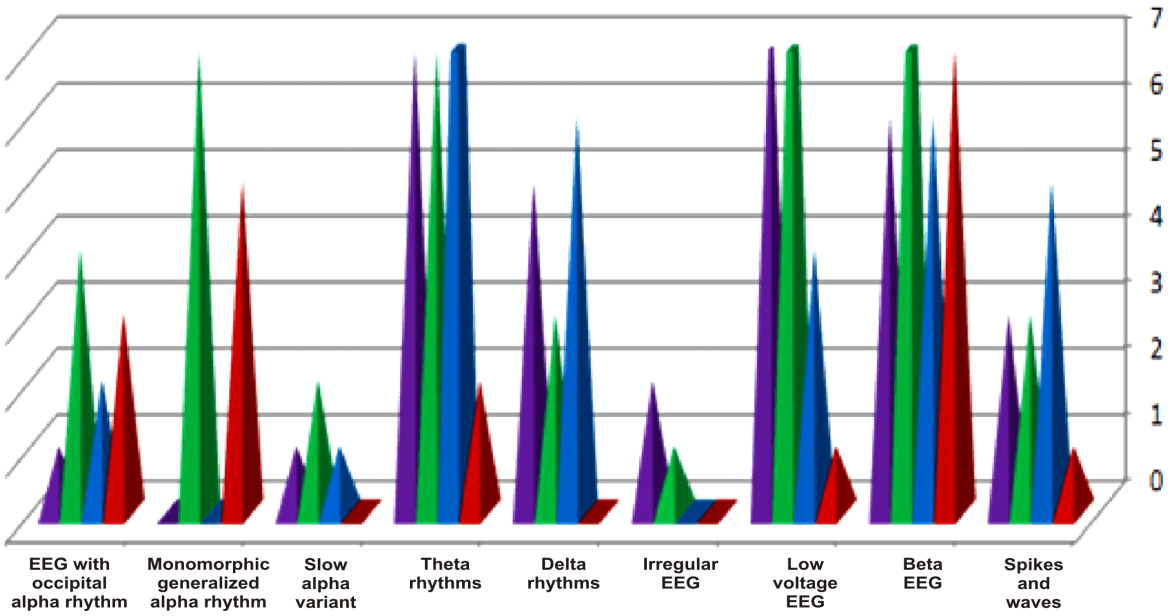

Figure 7 – *EEG in the study groups (1, 2, 3 and 4), total number of 55 children (29 boys and 26 girls).*

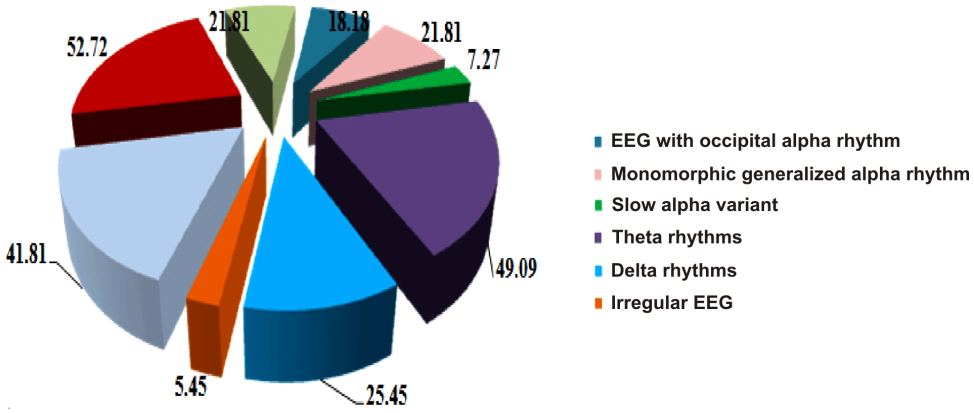

Figure 8 – *EEG in the study groups (1, 2, 3 and 4) for the total number of 55 children.*

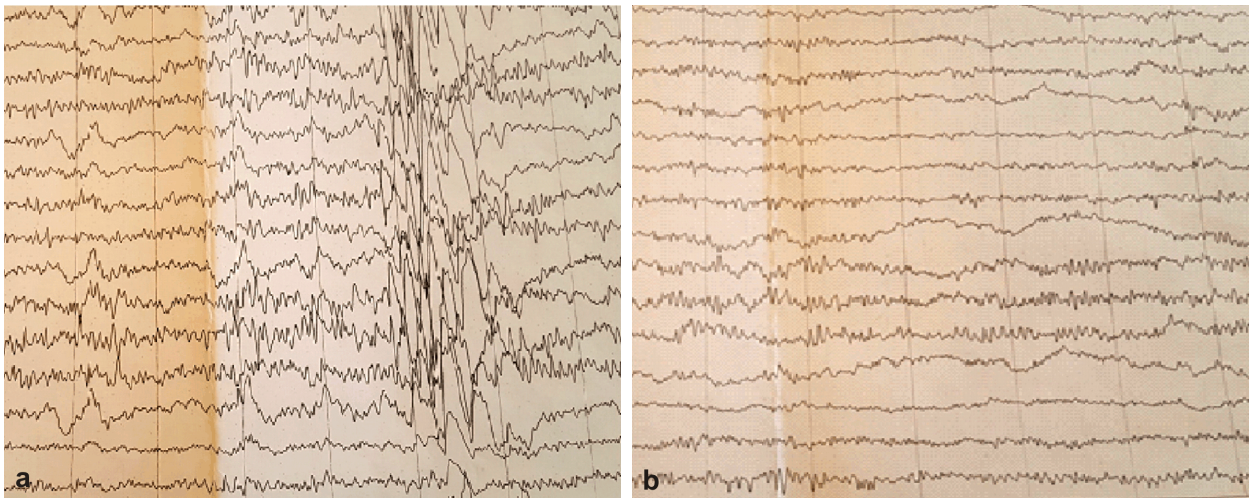

Figure 9 – *(a) EEG with paroxysmal discharges of peak-wave complexes; (b) EEG with forced normalization.*

MR spectroscopy results

Through the MR spectroscopy, we found modified values and concentrations of the cerebral metabolites for the groups of patients with epilepsy, convulsive seizures (in their medical personal history) – group 1, who developed in time a diagnosis of schizophrenia but also group 3, the UHR for psychosis patients group in comparison with the healthy group 5: high GABA values, especially in the hippocampus and thalamus, in temporal lobe epilepsy and in the frontal lobe in idiopathic generalized epilepsy, glutamate values especially in the frontal cortex, identifying brain lesions and GABA being a key component for abnormal hyperexcitability in epilepsy;

low NAA and *N*-acetylaspartylglutamate (NAAG) values; increased Glx and reduction of *N*-acetylaspartate + *N*-acetylaspartylglutamate (NAAt) in the frontal lobe, in idiopathic generalized epilepsy (IGE) (Figures 10 and 11).

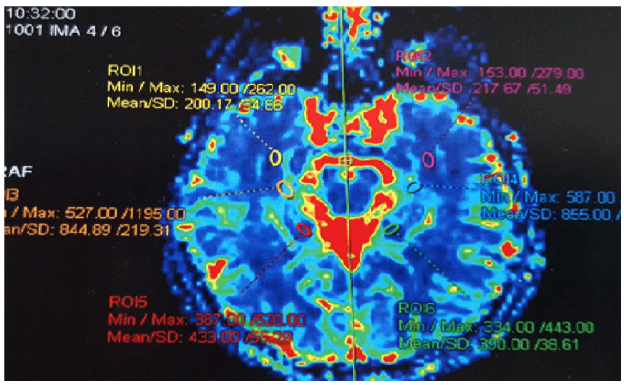

Figure 10 – ***Results for the MR spectroscopy brain metabolites concentrations in group 1, with epilepsy and with further schizophrenia onset.***

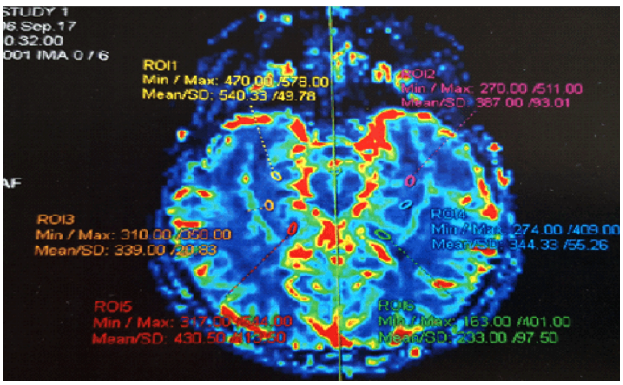

Figure 11 – ***Results for the MR spectroscopy brain metabolites concentrations in group 3, with epilepsy and UHR for psychosis.***

We also observed high values for the glutamate/glutamine, lactate/NAA, glutamate/Cr, Cho/Cr and low values for NAA/Cr, NAA/Cho, NAA/Cho + Cr ratios, showing the bilateral but dominant left hippocampal abnormalities especially in NAA/Cr, and low thalamic GABA/Cr ratio, in comparison with the healthy controls.

So that median right NAA/Cr 0.78, left 0.6 and normal values NAA/Cr > or = 1.

Also, the metabolite ratios Glx/NAAt and Glx/Ins showed elevation in IGE, in the frontal lobes and the thalami NAA/Cr were significantly decreased, as compared with healthy controls (p<0.001) (Figure 12).

These spectral abnormalities reflect the neuronal loss and damage.

The parieto-occipital cerebral lesions were captured through the increase of the values of Lactate, Cho, NAA and Glx.

The results were also suggestive for frontal and parieto-occipital bilateral cerebral lesions, with the characteristics of gray matter heterotopy – specific for migration disorders of the cortex in the embryological period (Figure 13).

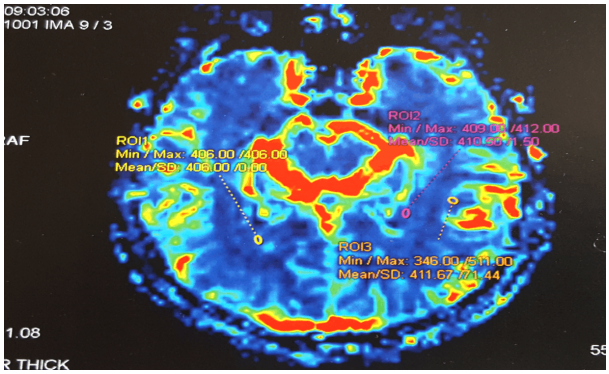

Figure 12 – ***Results for the MR spectroscopy brain metabolites concentrations in groups 1 and 3, with epilepsy.***

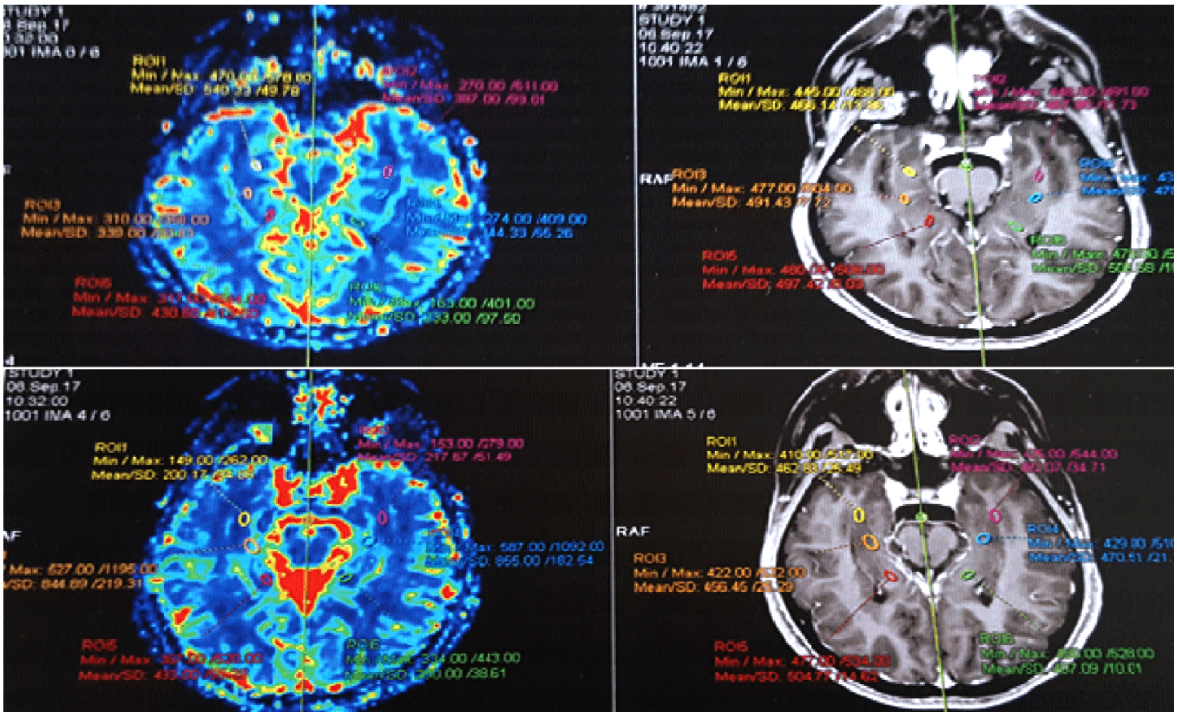

Figure 13 – ***Comparative results for the MR spectroscopy brain metabolites concentrations in group 1 (up) and in group 3 (down) with epilepsy.***

We also noticed strong negative correlations between GABA and NAA/Cr ratio, increased GABA correlated with decreasing NAA/Cr – Pearson's correlations (p<0.001).

Also, we found increased values for myo-inositol and glutathione, specific for edema and neuronal injury.

We detected reduction in the NAA signal, 15% increase in the Cr signal and 25% increase in the Cho signal (Figure 14).

Through applying the Pearson's test, we obtained as correlations' results, for the four groups, the following statistical significant positive correlations (Table 1).

Therefore, the highest correlations were in the groups G1 – with epilepsy history and G2 – UHR for psychosis with epilepsy history for: EEG abnormalities and earlier psychosis onset age, and MR spectroscopy metabolite's modifications and between positive family history and early psychosis onset age; mother's schizophrenia (SZ) and youngest age of psychosis onset; respectively EEG normalization and psychosis onset.

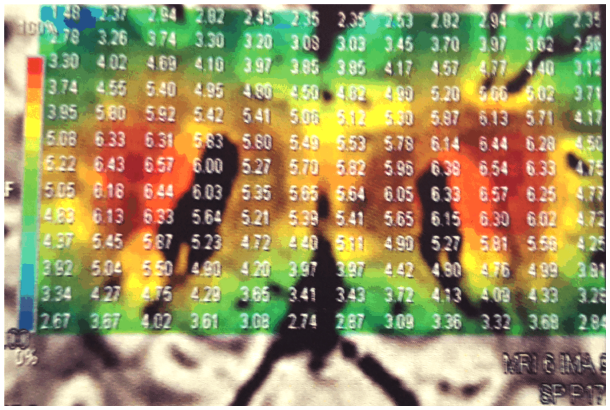

Figure 14 – ***MR spectroscopy matrix quantifying the concentrations of brain metabolites captured.***

Table 1 – ***Spearman's correlations transformed z, between the EEG abnormalities, the psychosis onset, the MR spectroscopy metabolites' modifications and the positive family history, for the studied groups***

Correlations	Patients with schizophrenia						UHR for psychosis					
	G1 with epilepsy history			*G2 without epilepsy history*			*G3 with epilepsy history*			*G4 without epilepsy history*		
	*r**	*z***	*z-STD***	*r**	*z***	*z-STD***	*r**	*z***	*z-STD***	*r**	*z***	*z-STD***
EEG abnormalities – Earlier psychosis onset age	**.969**	.511	.377	.318	.359	.383	**.974**	.856	.699	.264	.186	.432
EEG abnormalities – Earlier SZ onset age	**.987**	.345	.305	.221	.321	.263	**.982**	.189	.185	.119	.235	.177
EEG abnormalities – MR spectroscopy metabolite's modifications	**.985**	.841	.679	.653	.711	.709	**.989**	.621	.564	.387	.358	.354
Positive personal history for epilepsy – Early psychosis onset age	**.977**	.654	.308	.534	.431	.307	**.985**	.424	.221	.225	.115	.287
Mother's SZ – Youngest age of psychosis / SZ	**.969**	.733	.533	.387	.236	.532	**.987**	.311	.386	.311	.218	.326
EEG normalization – Psychosis onset	**.975**	.543	.389	.365	.342	.356	**.999**	.289	.127	239	.387	.249

EEG: Electroencephalography; MR: Magnetic resonance; UHR: Ultra high-risk; SZ: Schizophrenia; *r*: Spearman's rank correlation coefficient (rho); *z*: Transformed values; STD: Standard deviation; *: Coefficient of determination; **: Coefficient of non-determination.

Discussion

This study is important, especially in the context that there is a lack of studies on children and adolescents with UHR for psychosis, having a history of convulsive seizures/epilepsy and on schizophrenia pediatric patients with epilepsy and because valuable neuroimagistic MR spectroscopy correlations are captured.

This study has implications for the neurodevelopmental model of schizophrenia, which posts that brain damage during development increases the liability to this disorder. So that, a neurodevelopmental lesion increases the risk for this condition. Epileptic seizures damage the brain and a greater number of seizures results in damage to the brain severe enough to induce the symptoms of schizophrenia [2]. Therefore, the onset of schizophrenia would correspond to the dynamical process of the dysfunction of moving from surface to the profound levels of the brain.

Previous studies have demonstrated an increased prevalence of schizophrenia and schizophrenia-like psychosis in patients with epilepsy [11]. In their view, if family history of epilepsy, also raised the risk of schizophrenia, this suggested that genetic or environmental factors shared by families might increase the risk for both conditions.

In our study, evaluating the schizophrenia cases with onset during adolescence, retrospectively, we found an increased risk for schizophrenia in patients with a history of epilepsy (30% cases).

Future studies aiming to identify the environmental factors, particularly childhood infections or potential genes that predispose both to febrile seizures and schizophrenia may be fruitful. Certain genes that increase the risk of epilepsy might also increase the risk of schizophrenia [2–5, 11, 24].

Some of the strengths of our study are the prospective observation of the children with convulsive seizures, who have a positive family history of epilepsy, that is highly needed; and the evaluation of the cases of children with a family history of epilepsy without a personal history of epilepsy.

Longitudinal magnetic resonance imaging (MRI) studies of normal aging have demonstrated heterogeneous patterns of cortical maturation in the developing brain [25]. Frontal and occipital regions have thinner cortex with increasing age, while this has not been shown for temporal regions.

In a longitudinal study of childhood-onset SZ, over five years, the patients showed reduction of gray matter volume first in parietal, and later in temporal and prefrontal cortical areas compared to the healthy children [25]. So that, the psychotic symptoms emerge as a manifestation of these neurobiological dysfunctions [11, 21].

It is significant to study the UHR populations. In line with other existing studies, the UHR criteria are: attenuated symptoms, having experienced sub-threshold (less severe) psychotic symptoms in the past year; brief limited intermittent psychotic symptoms, having experienced episodes of frank psychotic symptoms for less than a week, which have solved naturally; trait and state risk factor, having a first degree relative with a psychotic disorder or meeting diagnostic criteria for schizotypal personality disorder and having experienced a significant decrease in social functioning over the past year [3].

About 35% of cases detected in this way would subsequently meet diagnostic criteria for psychotic disorder within a year despite interventions [26] or about 16% [2, 3].

There is also extensive evidence, which suggests that this group commonly shows neurobiological markers of psychotic endophenotypes [27]. 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 [3, 5].

Both schizophrenia and bipolar disorder are heritable, a high rate of those diagnoses being found in the offspring, this is the reason why the psychiatric family history is important to be known for the UHR patients [5]. The chronic illness course, the progressive grey matter decline during early disease stages formed the basis for research on the psychosis risk syndrome (PRS), known as "clinical high-risk" (CHR) or UHR or prodrome [3, 5, 9, 24, 28].

Some valuable studies reported a rate of transition to psychosis in the UHR patients of 41% by 12 months and 50% by 24 months. Other significant studies suggest a conversion rate to psychosis of 64% in the UHR patients [3, 9].

Our main focus was to investigate the neurobiological, EEG, neuroimagistic and clinical aspects, for the UHR population in order to have a better management of intervention and to prevent, decline or postpone the transition to diagnosable psychosis.

We considered the ethical foundation for 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 pediatric population [29–31].

Further studies are needed that evaluate the empirical relationships among different EEG abnormalities in schizophrenia and the relationships of the individual EEG abnormalities to neuroimaging, neurocognitive, biochemical and molecular genetic data obtained from the same subjects [4, 6, 7, 32].

Studies utilizing the EEG in conjunction with other research tools will ultimately lead to a more comprehensive description and better understanding of the cognitive and brain functions that are altered in schizophrenia.

EEG measures ongoing electrical brain activity and provides a possible basis for endophenotypes of brain function associated with psychosis [33]. Several such measures are highly heritable [34].

Relatively little research has been conducted on resting QEEG activity in correlation with MR spectroscopy, in patients with psychosis, especially in populations at risk for the illness and results have been inconsistent and sometimes even contradictory [35, 36]. Nonetheless, psychotic patients generally exhibit increased slow wave QEEG activity in the delta (0.5–3.5 Hz) and theta (4–7 Hz) bands [37, 38], and decreased alpha (8–13 Hz) activity [37]. In terms of resting beta (14–30 Hz) activity, results are inconsistent, with studies reporting both decreased [39] and increased [37] activity, as well as no abnormalities in patients with psychosis [37–39]. It is therefore unclear whether resting QEEG represents a useful endophenotype for psychosis, which pleads for the need for further research in this area [7, 11, 12, 15, 19].

Based on past findings, it was hypothesized that amplitudes in delta and theta frequency bands would be increased, and amplitude in the alpha band would be reduced, in patients with psychosis as well as in populations at risk, compared to healthy controls. In the beta frequency band, no direction of abnormalities was predicted.

In our present study, we observed: generalized patterns of increased theta and delta activity, a decreased dimension complexity, as a result of the overall brain dysfunction; decreased alpha activity and reduced alpha peak frequencies; and paradoxical or "forced" EEG normalization for the UHR group of patients who developed psychosis [17]. Comparing group 1 (schizophrenia with epilepsy history) and group 2 (without schizophrenia with epilepsy history), in our study, there is some reason to suspect that there are two clinical phenotypes of schizophrenia: one phenotype associated with a pattern of longstanding developmental abnormality, in which the actual psychotic episode develops after some years of preexisting abnormality. Early onset is associated with a worse outcome. In the group 2, the disorder develops in the context of previously normal development.

We also noticed, in our study, that from the epileptic seizures, 55% were focal seizures, especially partial complex seizures, so that (temporal lobe epilepsy) would be more likely to influence the risk of schizophrenia. In 45% of the cases, we have seen generalized tonic-clonic convulsive seizures or atypical absence type seizures.

We also observed the association between a family history of psychosis in UHR groups (65% from the cases with family history, had schizophrenia and 35% bipolar disorder with psychotic symptoms).

In our study, the early onset (13–15 years) was seen for the children with mothers with SZ, especially if the mother's SZ was diagnosed before the birth of the child.

Also, we noticed in 70% of the cases in group 1, an

association between febrile seizures during childhood and schizophrenia. For the children with febrile seizures in the period 1–3 years, the diagnosis of schizophrenia was put later in the period 16–17 years. The phenomenon of balance between the inter-crises psychic disorders and epileptic seizures, under antiepileptic treatment, concomitantly with the onset of psychosis, is called "forced normalization of EEG". So that, other studies observed that through the interrupting of convulsive seizures sometimes an inhibition of the dopamine incorporation at the level of thalamus is produced, bringing the psychosis onset with it [11, 15, 19].

Concerning the MR spectroscopy, our obtained results are in line with some other existing studies. Therefore, concerning the group with temporal lobe epilepsy, NAA changes were specific to the epileptogenic zone [21, 40–43].

While it is not surprising, that metabolic dysfunction follows from uncontrolled seizure activity, it has also been known that oxidative stress can cause also abnormalities in GABA and glutamate. Therefore, Saransaari & Oja (1997) studied the mouse hippocampus with variable levels of peroxide stress and showed increase in basal GABA release, ranging from 30% to 550% [44]. These observations are of great interest for epilepsy, where GABA is thought to be a key component, underlying the abnormal hyperexcitability. In line with the high energetic cost of the neurotransmission and synaptic activity, according to the studies of Attwell & Laughlin (2001), we anticipated that GABA neurotransmission and the metabolic function might be correlated with the seizures onset zone [45].

Therefore, the GABA function might be in this case proconvulsant, like Woo *et al.* (2002) [46] and Palma *et al.* (2006) [47] suggested.

GABA can so become excitatory and can further propagate seizure-linked injury [22].

Other important MR spectroscopy metabolites identified for epilepsy included glutamate, myo-inositol, lactate and glutamine. Glutamate and GABA, in particular, are important targets, given their role in neurotransmission [48–50].

MR spectroscopy has long been proposed to be useful for non-invasively evaluating the process of epileptogenesis, also according with some existing studies, captured in Stagg *et al.* [20, 21, 48, 49, 51].

Another study of Filibian *et al.* (2012) found progressive increases in myo-inositol and glutathione with decreases in NAA in epilepsy, characterizing edema and neural injury [51–53].

This interesting studies raise the question of what these changes might mean for epileptogenesis. So, some studies and also, animal model studies, have identified changes in many of these compounds that are linked with epileptogenesis and seizures-related injury [54–56].

Also, idiopathic generalized epilepsy was associated, in our study, in line with other existing studies, with bilateral frontal lobe metabolite changes. Also, elevation in Glx was observed, which may imply increased neuronal excitability, whereas reduction of NAAt suggesting neuronal dysfunction [22, 50].

So that, brain metabolism as well as synaptic activity influences the MR spectroscopy results.

Our obtained results are in line with the study of Simister *et al.* (2003) on 21 patients and 17 controls with IGE [21, 52, 57]. So that, especially in the frontal lobes, glutamate and glutamine were increased, NAA and inositol were decreased in patients compared with controls.

On the other side, Mory *et al.* (2003) discovered significant decreases in thalamic NAA/Cr ratio, in the patients compared with controls. These two studies also provided evidence for thalamic and frontal lobe dysfunction in patients with IGE. This data lends some support to the thalamocortical hypothesis for the generation of epileptiform discharges in generalized epilepsy [53–55, 58].

Further research is needed in the field of psychiatry/ child psychiatry especially, in order to develop some integrative correlations of the neurobiological, EEG abnormalities, neuroimagistic modifications and their clinical application.

The results of our research, plead for the utility of this modern integrative approach, which represents the only valid path for the future treatment management of high quality. If technical advances would permit simultaneous acquisition of MR spectroscopy, from several compounds in multiple brain regions, with ongoing EEG recording, pharmacological challenges might be cleared, in order to address these complex issues. With improved rapid encoding methods, we anticipate that the sensitive detection of key metabolites will enable a deeper understanding of epilepsy and schizophrenia and how they can be better clinically managed.

Conclusions

Epilepsy or febrile seizures in an individual increases the risk of schizophrenia and the epileptic seizures damage the brain and a greater number of seizures results in a damage to the brain, severe enough to induce the symptoms and signs of schizophrenia. The increased risk of schizophrenia is associated with both a personal history of epilepsy and familial history of psychosis that was stronger. So that, the fingerprinting of the EEG, neurobiological and MR spectroscopy markers, represent strongly predictive factors of the clinical evolution in child psychoses, especially schizophrenia and UHR categories. The evaluation through EEG and of neuroimagistic markers in psychotic and UHR patients, proved high clinical utility in prevention, early detection and intervention. This integrative approach, of investigating: the biological markers of basic pathophysiological mechanisms, EEG abnormalities; and the neuroimagistic correlations in schizophrenia, epilepsy and UHR categories, can be utilized as a fruitful path of understanding etiology and pathophysiology and may lead to improvements in early detection and more effective and targeted treatment of schizophrenia. Our research was a proof that sustains this complex integrative approach, as a successful path of care and intervention.

Conflict of interests

The authors declare that they have no conflict of interests.

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Author contribution

Lavinia Maria Hogea has equal contribution and thus shares first authorship.

References

[1] Rapoport JL, Addington AM, Frangou S, Psych MR. The neurodevelopmental model of schizophrenia: update 2005. Mol Psychiatr, 2005, 10(5):434–449.
[2] Thaker GK, Carpenter WT (eds). The year in schizophrenia. Vol. 1, Clinical Publishing, Atlas Medical Publishing Ltd., Oxford, UK, 2007, 20–54.
[3] Yung AR, Phillips LJ, Yuen HP, McGorry PD. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophr Res, 2004, 67(2–3):131–142.
[4] Coburn KL, Lauterbach EC, Boutros NN, Black KJ, Arciniegras DB, Coffey CE. The value of quantitative electroencephalography in clinical psychiatry: a report by the Committee on Research of the American Neuropsychiatric Association. J Neuropsychiatry Clin Neurosci, 2006, 18(4): 460–500.
[5] Correll CU, Hauser M, Auther AM, Cornblatt BA. Research in people with the psychosis risk syndrome: a review of the current evidence and future directions. J Child Psychol Psychiatry, 2010, 51(4):390–431.
[6] Gross A, Joutsiniemi SL, Rimon R, Appelberg B. Correlation of symptom clusters of schizophrenia with absolute powers of main frequency bands in quantitative EEG. Behav Brain Funct, 2006, 2:23.
[7] Gschwandtner U, Pflueger MO, Semenin V, Gaggiotti M, Riecher-Rössler A, Fuhr P. EEG: a helpful tool in the prediction of psychosis. Eur Arch Psychiatry Clin Neurosci, 2009, 259(5): 257–262.
[8] Lavoie S, Schäfer MR, Whitford TJ, Benninger F, Feucht M, Klier CM, Yuen HP, Pantelis C, McGorry PD, Amminger GP. Frontal delta power associated with negative symptoms in ultra-high risk individuals who transitioned to psychosis. Schizophr Res, 2012, 138(2–3):206–211.
[9] Ruhrmann S, Schultze-Lutter F, Salokangas RKR, Heinimaa M, Linszen D, Dingemans P, Birchwood M, Patterson P, Juckel G, Heinz A, Morrison A, Lewis S, Graf von Reventlow H, Klosterkötter J. Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. Arch Gen Psychiatry, 2010, 67(3):241–251.
[10] Merrin EL, Floyd TC. Negative symptoms and EEG alpha in schizophrenia: a replication. Schizophr Res, 1996, 19(2–3): 151–161.
[11] Qin P, Xu H, Laursen TM, Vestergaard M, Mortesen PB. Risk for schizophrenia and schizophrenia-like psychosis among patients with epilepsy: population based cohort study. BMJ, 2005, 331(7507):23.
[12] Ranlund S, Nottage J, Shaikh M, Dutt A, Constante M, Walshe M, Hall MH, Friston K, Murray R, Bramon E. Resting EEG in psychosis and at-risk populations – a possible endophenotype? Schizophr Res, 2014, 153(1–3):96–102.
[13] Singh F, Pineda J, Cadenhead KS. Association of impaired EEG mu wave suppression, negative symptoms and social functioning in biological motion processing in first episode of psychosis. Schizophr Res, 2011, 130(1–3):182–186.
[14] van der Stelt O, Berger A. Application of electroencephalography to the study of cognitive and brain functions in schizophrenia. Schizophr Bull, 2007, 33(4):955–970.
[15] Vestergaard M, Pedersen CB, Christensen J, Madsen KM, Olsen J, Mortesen PB. Febrile seizures and risk of schizophrenia. Schizophr Res, 2005, 73(2–3):343–349.
[16] Winterer G, Egan MF, Rädler T, Hyde T, Coppola R, Weinberger DR. An association between reduced interhemispheric EEG coherence in the temporal lobe and genetic risk for schizophrenia. Schizophr Res, 2001, 49(1–2):129–143.
[17] Wolf P. Acute behavioral symptomatology at disappearance of epileptiform EEG abnormality. Paradoxical or "forced" normalization. Adv Neurol, 1991, 55:127–142.
[18] Zietsch BP, Hansen JL, Hansell NK, Geffen GM, Martin NG, Wright MJ. Common and specific genetic influences on EEG power bands delta, theta, alpha, and beta. Biol Psychol, 2007, 75(2):154–164.
[19] Zimmermann R, Gschwandtner U, Wilhelm FH, Pflueger MO, Riecher-Rössler A, Fuhr P. EEG spectral power and negative symptoms in at-risk individuals predict transition to psychosis. Schizophr Res, 2010, 123(2–3):208–216.
[20] Bernasconi A, Bernasconi N, Natsume J, Antel SB, Andermann F, Arnold DL. Magnetic resonance spectroscopy and imaging of the thalamus in idiopathic generalized epilepsy. Brain, 2003, 126(Pt 11):2447–2454.
[21] Stagg C, Rothman D (eds). Magnetic resonance spectroscopy: tools for neuroscience research and emerging clinical applications. 1st edition, Academic Press–Elsevier, San Diego, CA, USA, 2014, 62–83.
[22] Simister RJ, McLean MA, Barker GJ, Duncan JS. A proton magnetic resonance spectroscopy study of metabolites in the occipital lobes in epilepsy. Epilepsia, 2003, 44(4):550–558.
[23] Connelly A, Jackson GD, Duncan JS, King MD, Gadian DG. Magnetic resonance spectroscopy in temporal lobe epilepsy. Neurology, 1994, 44(8):1411–1417.
[24] Nussbaum L, Ogodescu A, Hogea L, Nussbaum L, Zetu I. Risk factors and resilience in the offspring of psychotic parents. Revista de Cercetare şi Intervenţie Socială, 2017, 56:114–122.
[25] Thompson PM, Sowell ER, Gogtay N, Giedd JN, Vidal CN, Hayashi KM, Leow A, Nicolson R, Rapoport JL, Toga AW. Structural MRI and brain development. Int Rev Neurobiol, 2005, 67:285–323.
[26] Ruhrmann S, Schultze-Lutter F, Klosterkötter J. Early detection and intervention in the initial prodromal phase of schizophrenia. Pharmacopsychiatry, 2003, 36(Suppl 3):S162–S167.
[27] Pantelis C, Yücel M, Bora E, Fornito A, Testa R, Brewer WJ, Velakoulis D, Wood SJ. Neurobiological markers of illness onset in psychosis and schizophrenia: the search for a moving target. Neuropsychol Rev, 2009, 19(3):385–398.
[28] Chuma J, Mahadun P. Predicting the development of schizophrenia in high-risk populations: systematic review of the predictive validity of prodromal criteria. Br J Psychiatry, 2011, 199(5):361–366.
[29] Andreescu N, Nussbaum L, Hogea LM, Grădinaru R, Muntean C, Ştefănescu R, Puiu M. Antipsychotic treatment emergent adverse events in correlation with the pharmacogenetic testing and drug interactions in children and adolescents with schizophrenia and bipolar disorder. Farmacia, 2016, 64(5): 736–744.
[30] Nussbaum L, Hogea LM, Călina D, Andreescu N, Grădinaru R, Ştefănescu R, Puiu M. Modern treatment approaches in psychoses. Pharmacogenetic, neuroimagistic and clinical implications. Farmacia, 2017, 65(1):75–81.
[31] Nussbaum LA, Andreescu N, Nussbaum L, Gradinaru R, Puiu M. Ethical issues related to early intervention in children and adolescents with ultra high risk for psychosis: clinical implications and future perspectives. Rev Rom Bioet, 2014, 12(3): 64–81.
[32] Ilmoniemi RJ, Aronen HJ. Cortical excitability and connectivity reflected in fMRI, MEG, EEG, and TMS. In: Moonen CTW, Bandettini PA (eds). Functional MRI (Medical Radiology / Diagnostic Imaging). Springer Verlag, Berlin–Heidelberg–New York, 2000, 453–463.
[33] Hall MH, Smoller JW. A new role for endophenotypes in the GWAS era: functional characterization of risk variants. Harv Rev Psychiatry, 2010, 18(1):67–74.
[34] Tang Y, Chorlian DB, Rangaswamy M, Porjesz B, Bauer L, Kuperman S, O'Connor S, Rohrbaugh J, Schuckit M, Stimus A, Begleiter H. Genetic influences on bipolar EEG power spectra. Int J Psychophysiol, 2007, 65(1):2–9.
[35] Gross A, Joutsiniemi SL, Rimon R, Appelberg B. Correlation of symptom clusters with absolute powers of main frequency bands in quantitative EEG. Behav Brain Funct, 2006, 2:23.
[36] Boutros NN, Arfken C, Galderisi S, Warrick J, Pratt G, Iakono W. The status of spectral EEG abnormality as a diagnostic test for schizophrenia. Schizophr Res, 2008, 99(1–3):225–237.

[37] Begić D, Popović-Knapić V, Grubišin J, Kosanović-Rajačić B, Filipčić I, Telarović I, Jakovljević M. Quantitative electroencephalography in schizophrenia and depression. Psychiatr Danub, 2011, 23(4):355–362.
[38] Hong LE, Summerfelt A, Mitchell BD, O'Donnell P, Thaker GK. A shared low-frequency oscillatory rhythm abnormality in resting and sensory gating in schizophrenia. Clin Neurophysiol, 2012, 123(2):285–292.
[39] John ER, Prichep LS, Alper KR, Mas FG, Cancro R, Easton P, Sverdlov L. Quantitative electrophysiological characteristics and subtyping of schizophrenia. Biol Psychiatry, 1994, 36(12): 801–826.
[40] de la Fuente-Sandoval C, Reyes-Madrigal F, Mao X, León-Ortiz P, Rodríguez-Mayoral O, Solís-Vivanco R, Favila R, Graff-Guerrero A, Shungu DC. Cortico-striatal GABAergic and glutamatergic dysregulations in subjects at ultra-high risk for psychosis investigated with proton magnetic resonance spectroscopy. Int J Neuropsychopharmacol, 2015, 19(3):pyv105.
[41] Brugger S, Davis JM, Leucht S, Stone JM. Proton magnetic resonance spectroscopy and illness stage in schizophrenia – a systematic review and meta-analysis. Biol Psychiatry, 2011, 69(5):495–503.
[42] Egerton A, Stone JM, Chaddock CA, Barker GJ, Bonoldi I, Howard RM, Merritt K, Allen P, Howes OD, Murray RM, McLean MA, Lythgoe DJ, O'Gorman RL, McGuire PK. Relationship between brain glutamate levels and clinical outcome in individuals at ultra high risk of psychosis. Neuropsychopharmacology, 2014, 39(12):2891–2899.
[43] Wood SJ, Kennedy D, Phillips LJ, Seal ML, Yücel M, Nelson B, Yung AR, Jackson G, McGorry PD, Velakoulis D, Pantelis C. Hippocampal pathology in individuals at ultra-high risk for psychosis: a multi-modal magnetic resonance study. Neuroimage, 2010, 52(1):62–68.
[44] Saransaari P, Oja SS. Enhanced taurine release in cell-damaging conditions in the developing and ageing mouse hippocampus. J Neurosci, 1997, 79(3):847–854.
[45] Attwell D, Laughlin SB. An energy budget for signaling in the grey matter of the brain. J Cereb Blood Flow Metab, 2001, 21(10):1133–1145.
[46] Woo N, Lu J, England R, McClellan R, Dufour S, Mount DB, Deutch AY, Lovinger DM, Delpire E. Hyperexcitability and epilepsy associated with disruption of the mouse neuronal-specific K-Cl cotransporter gene. Hippocampus, 2002, 12(2): 258–268.
[47] Palma E, Amici M, Sobrero F, Spinelli G, Di Angelantonio S, Ragozzino D, Mascia A, Scoppetta C, Esposito V, Miledi R, Eusebi F. Anomalous levels of Cl^- transporters in the hippocampal subiculum from temporal lobe epilepsy patients make GABA excitatory. Proc Natl Acad Sci U S A, 2006, 103(22): 8465–8468.
[48] Kraguljac NV, White DM, Reid MA, Lahti AC. Increased hippocampal glutamate and volumetric deficits in unmedicated patients with schizophrenia. JAMA Psychiatry, 2013, 70(12):1294–1302.
[49] Allen P, Chaddock CA, Egerton A, Howes OD, Barker G, Bonoldi I, Fusar-Poli P, Murray R, McGuire P. Functional outcome in people at high risk for psychosis predicted by thalamic glutamate levels and prefronto-striatal activation. Schizophr Bull, 2015, 41(2):429–439.
[50] Marsman A, Mandl RC, Klomp DW, Bohlken MM, Boer VO, Andreychenko A, Cahn W, Kahn RS, Luijten PR, Hulshoff Pol HE. GABA and glutamate in schizophrenia: a 7 T ^{1}H-MRS study. Neuroimage Clin, 2014, 6:398–407.
[51] Filibian M, Frasca A, Maggioni D, Micotti E, Vezzani A, Ravizza T. *In vivo* imaging of glia activation using ^{1}H-magnetic resonance spectroscopy to detect putative biomarkers of tissue epileptogenicity. Epilepsia, 2012, 53(11):1907–1916.
[52] Nussbaum LA, Hogea LM, Andreescu NI, Grădinaru RC, Puiu M, Todica A. 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. Rom J Morphol Embryol, 2016, 57(3):959–967.
[53] Gomes WA, Lado FA, de Lanerolle NC, Takahashi K, Pan C, Hetherington HP. Spectroscopic imaging of the pilocarpine model of human epilepsy suggests that early NAA reduction predicts epilepsy. Magn Reson Med, 2007, 58(2):230–235.
[54] Maudsley AA, Domenig C, Ramsay RE, Bowen BC. Application of volumetric MR spectroscopic imaging for localization of neocortical epilepsy. Epilepsy Res, 2010, 88(2–3):127–138.
[55] Pan JW, Spencer DD, Kuzniecky R, Duckrow RB, Heterington H, Spencer SS. Metabolic networks in epilepsy by MR spectroscopic imaging. Acta Neurol Scand, 2012, 126(6):411–420.
[56] Seidenberg M, Kelly KG, Parrish J, Geary E, Dow C, Rutecki P, Hermann B. Ipsilateral and contralateral MRI volumetric abnormalities in chronic unilateral temporal lobe epilepsy and their clinical correlates. Epilepsia, 2005, 46(3): 420–430.
[57] Simister RJ, McLean MA, Barker GJ, Duncan JS. Proton MRS reveals frontal lobe metabolite abnormalities in idiopathic generalized epilepsy. Neurology, 2003, 61(7):897–902.
[58] Mory SB, Li LM, Guerreiro CAM, Cendes F. Thalamic dysfunction in juvenile myoclonic epilepsy: a proton MRS study. Epilepsia, 2003, 44(11):1402–1405.

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