The role of substance use disorder and autoimmunity in juvenile psychoses

PhD thesis

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Pécs

2022

Contents

1. List of abbreviations

2-AG:	2-arachydonoylglycerol
Amp:	amphiphysin
CASPR2:	contractin-associated protein 2
CB1:	cannabinoid 1 receptor
CB2:	cannabinoid 2 receptor
CK:	creatine kinase
CRP:	C-reactive protein
CS:	citrate synthase
CSF:	cerebrospinal fluid
CT:	computed tomography
EEG:	electroencephalography
LDH:	lactate dehydrogenase
LGI1:	leucine-rich glioma-inactivated protein 1
MDMA:	3,4-methylenedioxymethamphetamine
MRI:	magnetic resonance imaging
NMDA:	N-methyl-D-aspartate
NPS:	new psychoactive substances
OGP:	oligoclonal gammopathy
PANSS:	Positive and Negative Syndrome Scale
PEA:	palmithoylethanolamid
Rec:	recovering
SCRA:	synthetic cannabinoid receptor agonist
SOX1:	sry-like high mobility group box protein1
VGKC:	voltage-gated potassium channel

2. Introduction

Psychosis is a disease indicating the dysfunctional functioning of the brain, during which the patient loses an adequate connection with reality. A psychotic person is unable to perceive reality and this affects their behavior, emotional world and thinking. During the symptomatology, positive, negative and general symptoms can also appear, which can be evaluated using the PANSS (Positive and Negative Syndrome Scale) scale.

In the vast majority of cases, its etiology is still unclear. The background can be psychiatric diseases (schizophrenia, schizoaffective disorder, bipolar disorder), but it can also be associated with organic diseases (encephalitis, epilepsy, autoimmune diseases). In clinical practice, the exact pathological factor underlying most new-onset psychoses has not been proven. Psychosis is usually a multifactorial disease, where the combination of several factors creates the actual clinical picture, in addition to genetic factors, environmental factors also play a significant role in the development of the disease. As schizophrenia research and related laboratory tests have developed in recent years, the discovery of the autoimmune origin of psychosis has become a hot topic in psychiatry. The author examines a possible cause of the autoimmune origin of psychoses in this study.

Various illegal drugs can also induce psychotic symptoms. We can talk about drug-induced psychosis if the given psychotic state can be etiologically linked to substance use and the psychosis cannot be better explained by other psychotic states. In my study, I examined psychotic patients induced by a new psychoactive substance (NPS), the synthetic cannabinoid receptor agonist (SCRA).

In the case of autoimmune encephalitis, the disease often manifests in patients with psychotic symptoms. Two groups of autoimmune diseases of the central nervous system can be distinguished based on the point of attack of the antibodies. Based on the presence of autoantibodies, autoimmune encephalitis can be classified as encephalitis induced by cell surface autoantibodies or onconeural autoantibodies. Cell surface autoantibodies bind to synaptic receptors, ion channels, or other cell surface proteins. The best known of them is anti-N-methyl-D-aspartate (NMDA) receptor encephalitis. Onconeural autoantibodies are most often associated with a tumor and appear as paraneoplastic symptoms and can cause a disease like psychosis.

In the other part of the study, I examined the presence of natural autoantibodies among SCRA-induced psychotic young patients. Natural antibodies function as a link between the innate and the adaptive immune response, and with their proper functioning, they participate in the maintenance of effective defense and the tolerance of one's own body. Natural antibodies are present in healthy individuals without prior antigen stimulation as well as in patients with autoimmune diseases.

3. Objectives

I. I set out to study a rare etiological connection by examining a synthetic substance-using teenage patient with psychosis.

II. Teenagers and young adults treated with the diagnosis of SCRA-induced psychosis admitted to the PTE KK Pediatric Clinic and the PTE KK Psychiatric and Psychotherapy Clinic were prospectively examined. We set ourselves the goal of detecting autoimmunity in the background of drug-induced psychosis.

III. We examined the relationship between the severity of psychosis - which was characterized by the PANSS value- and the presence of anti-neuronal autoantibodies.

IV. In our work, we also examined the presence of natural antibodies and compared them with the severity of psychosis and the co-occurrence of anti-neuronal antibodies among these young adults and teenagers.

V. Our other goals included performing a comparative analysis with the duration of drug use, positive family history, polytoxicosis and the presence of the previously mentioned antibodies.

4. Case Report

4.1. Case presentation

A 17-year-old, previously healthy teenager was admitted to the Traumatology Department after a head injury of unknown origin. He did not remember what had happened to him and appeared to be under the influence of substances. In the Traumatology Department, he was behaving in a confused manner, and a 3 cm lacerated wound was found above his right eyebrow. His psychiatric history revealed that he was a drug user, particularly synthetic

cannabinoids. During the examination in the Traumatology Department a tonic-clonic seizure occurred, which was treated with intravenous benzodiazepines.

The acute computed tomography (CT) examination did not confirm a traumatic skull fracture or intracranial bleeding. His neurological examination yielded negative results. The toxicology test was positive for cannabinoids and benzodiazepines (the latter may have been caused by benzodiazepine therapy). Apart from slightly elevated transaminase and lactate dehydrogenase (LDH) values and a slight increase in white blood cell count, nothing else was detected in his laboratory tests, EEG test was negative. On the same day, he had a second generalized tonic-clonic seizure, lasting one or two minute and stopped spontaneously. He could not be contacted during the seizure. In the following days, his behavior worsened, he started walking naked on the ward, became aggressive, and had acoustic and visual hallucinations. In addition to the positive psychotic symptoms, his psychomotor skills slowed down, looked blank several times and had convulsion in the upper limb. Due to epileptic seizures, carbamazepine was applied. His consciousness was fluctuating, he became disoriented, and his agitation increased, which required repeated haloperidol pharmacotherapy. Control laboratory tests still confirmed moderately elevated transaminase values, elevated D-dimer and creatine kinase (CK) values.

During the observation period, his psychomotility changed, catatonic symptoms such as stupor and mutism appeared. After a week, he developed a hypnoid disorder, had more frequent and severe generalized tonic-clonic seizures, and required to admit him to the intensive care unit. The repeated EEG examination showed still a generalized slowing, there were no abnormalities on acute intracranial MRI. During the lumbar puncture, clear cerebrospinal fluid was discharged with medium pressure, the biochemical, microbiological and native cerebrospinal fluid (CSF) tests were negative. Further CSF diagnostic tests confirmed oligoclonal gammopathy. During indirect immunofluorescence, antibodies against NMDA receptors were revealed in the serum and CSF from the autoimmune encephalitis panel. He was treated with high-dose steroids (1 g/day) for five days, but his condition did not change significantly. So we performed plasmapheresis five times and his condition gradually improved after that. After the acute intensive period, he took gradually decreasing doses of steroids and antipsychotic drug (risperidone 1.5 mg/day) for a month, and he received benzodiazepines during this period. After 2 months, we discharged him from our department without symptoms, from where he received outpatient care.

After 6 months, he was again admitted to our emergency department due to convulsions, which occurred after he started using illicit drugs again. During his subsequent admissions to the emergency department, he behaved aggressively and escaped before laboratory tests, so we were unable to perform further diagnostic tests. The repeated drug test was negative for traditional drugs, but according to him, he continued to use synthetic cannabinoids

4.2. Discussion

From the description of the patient's medical history, it should be highlighted that in addition to the diagnosis of drug-induced psychosis in the background of new-onset psychosis, it is worth looking for other pathologies. In the case of the young synthetic drug user, anti-NMDA receptor antibodies were detected in both the serum and CSF, which confirmed the diagnosis of anti-NMDR receptor encephalitis in the background of the psychotic symptoms. In connection with the analysis of the course of the patient's disease, the possibility arose that drug use may play a key role in the development of encephalitis. We hypothesized that synthetic drugs could trigger autoimmune processes that can cause autoimmune diseases, including autoimmune encephalitis. Based on literature data, viral agents and tumors can be also behind autoimmune encephalitis. Synthetic substances can even generate autoimmune processes as epitopes of the immune system. The consequence of this process may be the appearance of anti-neuronal antibodies which can cause autoimmune encephalitis.

Illicit drug use often leads us to think that the symptoms are caused by the drug or even a withdrawal mechanism. Tonic-clonic seizures can also be caused by drug use in case of an endogenous tendency. Illicit drug abuse can even result in psychosis, which happened in our case (causing visual and acoustic hallucinations). However, in order to establish the correct diagnosis, it is important not to focus only on one anamnestic data. A head injury or drug use can cause disruption of the blood-brain barrier, and circulating immunoglobulins can enter the central nervous system. When immunoglobulins pass through the blood barrier, they recognize certain parts of the brain as foreign and can trigger autoimmune processes, resulting in encephalitis. Depending on the area in which they exert their effect, they cause a characteristic clinical picture. In the case of involvement of the temporal lobe, hypothalamus, and amygdala, it presents as limbic encephalitis, in the case of brainstem involvement as rhombencephalitis, and in the case of joint involvement of the brain and spinal cord as encephalomyelitis.

In inflammatory processes of the central nervous system, in addition to antibodies, other immunological mechanisms may also play a role in the maintenance of inflammation. Several studies have shown that cannabinoids exert immunomodulatory effects through the cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) receptors. CB1 receptors are mostly found in the central nervous system and regulate synaptic signaling, in this way they can mediate the psychoactive effects characteristic of cannabis use. Within the central nervous system, they are found in the highest density in the hypothalamus, cerebellum and basal ganglia. CB2 receptors were initially found in the periphery, especially in immune cells (macrophages and B cells), but they also appear to play an important role in immune mechanisms in the central nervous system. Within the central nervous system, they are also found on dendritic cells, which are one of the main antigen-presenting cells of the nervous system. Cannabinoids can also influence the immunoglobulin production of B-lymphocyte cells via the CB2 receptor. Furthermore, endocannabinoids found in the body are involved in B-cell mobilization during an immune response. CNS endocannabinoids include, for example, anandamide, 2-arachydonoylglycerol (2-AG) and palmithoylethanolamide (PEA), which have similar effects on cannabinoid receptors as THC or SCRA.

Studying the case, we came up with the hypothesis that synthetic cannabinoid use could be behind the autoimmune encephalitis either due to the previously mentioned mimicry mechanism or excessive stimulation of CB receptors. We started our further investigations to prove this claim.

5. Examination

5.1. Methods

The study was conducted prospectively on 22 patients treated with a diagnosis of SCRA-induced psychosis, and patient samples were collected between 2015 and 2020. All patients underwent a comprehensive psychiatric examination and assessment of psychotic symptoms on the PANSS scale. The use of PANSS values was necessary due to the numerical assessment of the severity of psychosis in individual patients, thereby making psychosis statistically analyzable. In our study, it was important that the patients' psychosis was etiologically linked to SCRA use. The patients included young adults and teenagers who were

admitted in a psychotic state after synthetic cannabinoid use. Teenagers and young adults (between 13 and 32 years old) took part in the research. Due to the small number of items on teenagers, we extended the study to the age group of young adults. In routine laboratory parameters, we found normal serum electrolytes, blood count, kidney and liver function, and the laboratory test did not indicate infection.

The general characteristics of the patients are summarized in Table 1. The table contains the statistically analyzed main clinical data of our study, such as age, sex, time of drug use, polytoxicosis, positive family history of addictions and finally the PANSS values.

Characteristics	Synthetic cannabinoid users (n=22)
Age (years), mean (SD)	17 (4.9)
Sex (male), n (%)	19 (86.4%)
Family history (positive for addiction), n (%)	5 (22.7%)
Polytoxicomania (yes), n (%)	9 (40.9%)
Drug use (month), mean (SD)	23.8 (23.5)
PANSS total, mean (SD)	55 (18)
PANSS general, mean (SD)	32.6 (8.7)
PANSS positive, mean (SD)	11.7 (7.6)
PANSS negative, mean (SD)	11.1 (5.5)

Table 1. Patients' characteristics

The general exclusion criteria was if the patient was previously treated with other known psychiatric diseases (e.g. schizophrenia, schizoaffective psychosis, bipolar disorder). The patient was also excluded if he suffered from an autoimmune disease or currently had an infection.

On the day of the examination, a peripheral venous blood sample was taken for laboratory examination. During the laboratory analysis, in addition to complete blood count, C-reactive protein (CRP), liver and kidney function, the presence of anti-neuronal and natural antibodies was examined. After the peripheral blood was collected for the immunological examination, the blood was coagulated for at least 30 minutes, and then centrifuged at 1000 x g for 10 minutes after arriving in the laboratory. Serum was removed and stored at -80°C until assays for autoantibodies were performed. After that, we showed the anti-neuronal autoantibodies and the anti-citrate synthase (anti-CS) among the natural autoantibodies by indirect immunofluorescence, immunoblotting and ELISA.

5.2. Results

Between 2015 and 2020, we were able to include 22 patients in the study among young people who used synthetic cannabinoids. A significant proportion of psychotic patients following the use of SCRA were young men (86.36%), this observation and distribution is the same as that read in the literature (Figure 1).

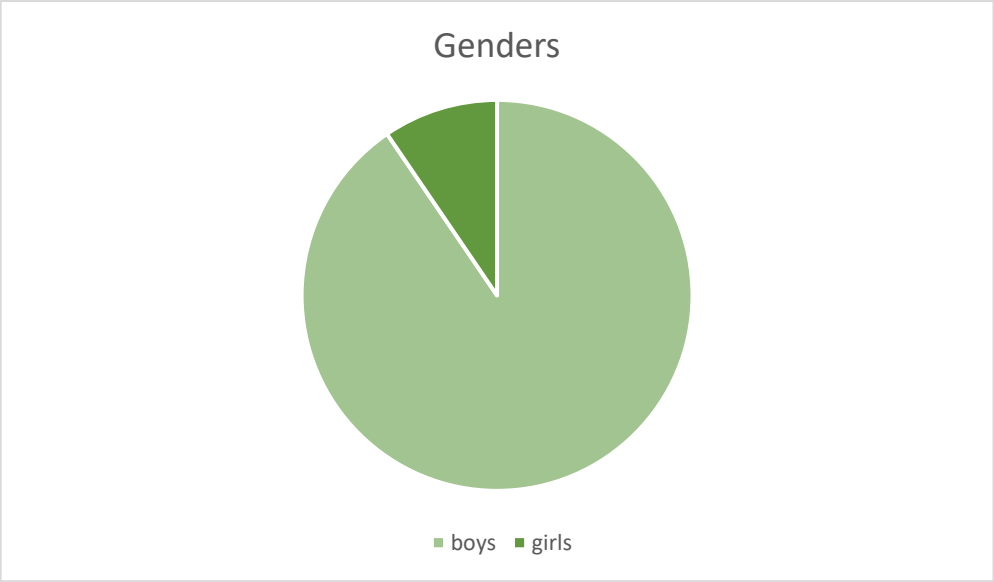

Figure 1: Gender distribution

The average age of the examined teenagers was 17,18 years (Figure 2). The average age of girls (15 years) was lower than that of boys (17.52 years), but given the small number of girls, statistical conclusions cannot be drawn from this.

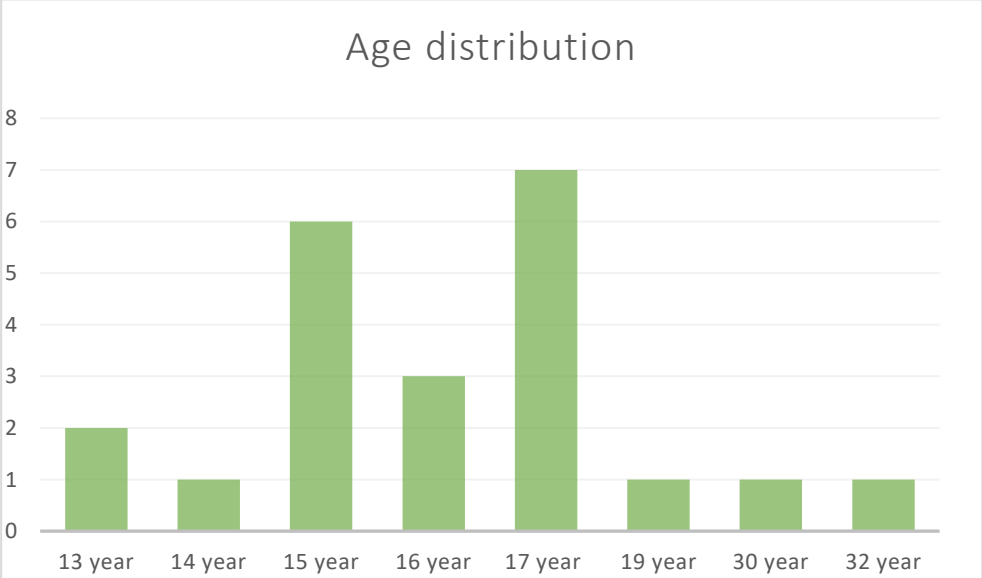

Figure 2: Age distribution

Looking at the anamnestic data, more than half of the patients (59.1%) only consumed SCRA, the rest of the patients had previously tried other drugs (40.9%). Other drugs included cannabis, other new types of psychoactive drugs, other psychostimulants (3,4-methylenedioxy methamphetamine (MDMA), cocaine, amphetamine), but also benzodiazepines. There was no difference in the time of drug use among SCRA users, half of the patients used illicit drugs within 1 year, while the other half used prohibited substances for more than 1 year, the time of drug use was unknown for 2 patients.

Eight of the 22 patient samples (36.4%) showed positive or borderline values for anti-neuronal autoantibodies. One patient (4.5%) was positive for antibody to CASPR2 derived from neuronal cell surface antibodies. One patient (4.5%) showed anti-ampiphysin (Amp) positivity and 6 patients (27.3%) showed borderline values for recoverin (Rec), Yo, Hu, sry-like high mobility group box protein 1 (SOX1) and Tr derived from onconeural antibodies. None of these patients was diagnosed with autoimmune encephalitis.

For statistical analyses, patients positive for anti-neuronal autoantibodies and borderline patients were considered as one group. We found no significant differences in PANSS-total, PANSS-positive, PANSS-negative and PANSS-general scores between patients with positive/borderline and negative results for these antibodies. The duration of substance use and the combination of other drugs with synthetic cannabinoids had no significant effect on anti-neuronal autoantibody positivity. (Figure 3)

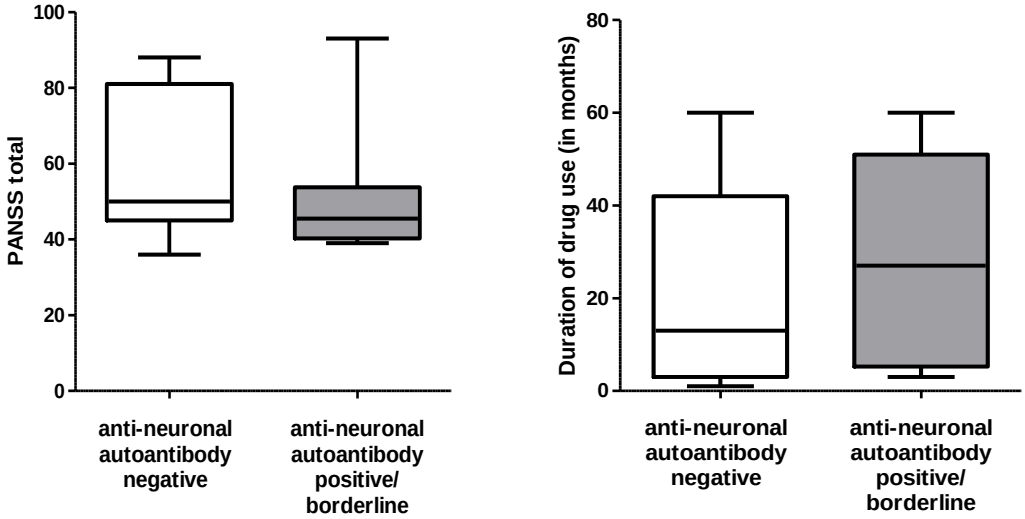

Figure 3: Correlation of PANSS total and the duration of drug use with the presence of anti-neuronal antibody (non-significant results)

We also investigated whether the levels of natural anti-CS IgM and IgG autoantibodies varied between patients with positive/borderline and negative anti-neuronal autoantibody results. We found no significant difference in the levels of anti-CS IgM (Figure 4A) or anti-CS IgG antibodies (Figure 4B) between the anti-neuronal autoantibody positive/borderline and negative groups, however, the anti-CS IgG showed a higher trend in patients with anti-neuronal autoantibody positive/borderline results than in patients with negative results (Figure 4B). Therefore we analyzed the ratio of anti-CS IgM to IgG among these patient groups and found it to be significantly lower (p=0.036) in the anti-neuronal autoantibody positive/borderline group than in the negative group (Figure 4C). After that, we evaluated the possible correlations between the amount of anti-CS IgM and IgG antibodies, their ratio and the severity of symptoms with PANSS-total, PANSS-positive, PANSS-negative and PANSS-general scores. Interestingly, the ratio of anti-CS IgM to IgG showed a significant negative correlation with the PANSS-positive score (p=0.04, r=-0.464). There was no significant correlation between the other PANSS values and the anti-CS values.

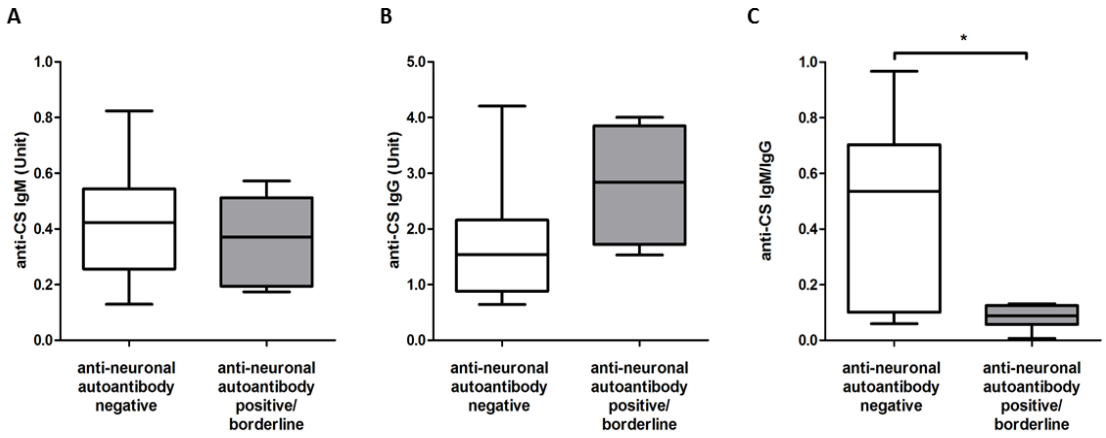

Figure 4: Difference in the ratio of anti-citrate synthase (CS) IgM and IgG autoantibodies in patients with positive/borderline (n=8) and negative (n=14) results for anti-neuronal autoantibodies

5.3. Discussion

The etiology of psychoses is heterogeneous, and many different diseases can be behind it. In addition to genetic vulnerability, environmental influences can also play a significant role in the development of the disease. In recent years, studies investigating the autoimmune origin of psychoses have come to the fore.

The diagnosis of autoimmune encephalitis presents real challenges, in the past they appeared more as paraneoplastic symptoms, but those encephalitis that manifest without a tumor hiding in the background are gaining more and more attention. The starting point of our investigation was a clinical case report, in connection with which we raised the role of synthetic drugs in inducing autoimmune processes, because in addition to the use of synthetic drugs, our patient had anti-NMDA receptor encephalitis with psychosis, causing significant differential diagnostic difficulties. Based on this, we considered it important to investigate whether autoimmune processes are prolonged in the background of drug-induced psychosis following SCRA use. To confirm or reject this, we planned our further studies, in connection with which we determined anti-neuronal antibodies and natural autoantibodies in young people suffering from drug-induced psychosis caused by synthetic drug use. The hypothesis, which arose during the case report, that synthetic drugs can cause autoimmune diseases, was clearly not proven during our investigation. During my work, I found no demonstrable correlation between the presence of anti-neuronal antibodies and the use of synthetic drugs in the studied population, however, in cases of positive and borderline anti-neuronal antibodies, the autoimmune origin cannot be ruled out. The examination of anti-neuronal antibodies is therefore not justified routinely in the case of new-onset juvenile psychosis.

The consumption of NPS has become very widespread in the last decade. The latest NPS, including cathinone derivatives and synthetic cannabinoids, have expanded in use and are well known, especially among the young population. In Europe, its prevalence varies between 0.1% and 1.5% in different countries. The availability of compounds changes rapidly and it is difficult to detect these substances with routine urine drug testing. Their purchase via the Internet is cheap, which is why the use of "legal drugs" among adolescents is widespread. SCRA users are generally low-educated and mostly men, correspondingly, 86.4% of the patients in our study were men. In addition to the psychostimulant effect of these drugs, acute toxicity and

drug-induced psychosis may also occur. Some toxicology reports have highlighted the following main characteristic psychiatric symptoms: toxic psychosis and delirium (40%), agitation (10%) and hallucinations (4-7%). In addition to central nervous system effects, they can also affect the functioning of other organs, acute kidney failure is increasingly being described after SCRA use. SCRA users had higher positive PANSS than THC users in the literature. The greater toxicity is due to pharmacological characteristics: SCRAs have 50-300 times greater affinity for CB1 than THC, and SCRAs are full agonists at CB1, whereas THC is only a partial agonist at the CB1 receptor. Cannabinoids can modulate immune responses in the brain and affect the number, proliferation and migration of B-lymphocyte cells. In our study, we found that 36.4% of patients with SCRA-induced psychosis showed positive or borderline anti-neuronal autoantibodies. Among the autoantibodies against neuronal cell surface antigens, the most studied is the anti-NMDA antibody, which is the most common antibody that can cause autoimmune encephalitis. None of the patients in our study had anti-NMDA receptor antibodies. Leucine-rich glioma-inactivated protein 1 (LGI1) and contractin-associated protein 2 (CASPR2) antibodies are currently classified as voltage-gated potassium channel complex (VGKC) antibodies and generally have the same clinical significance. There are cases when the anti-VGKC disease initially appeared with a schizophrenic type of psychiatric illness. In our study, only one patient had a borderline antibody against CASPR2, so cell surface autoantibodies appeared less frequently in the studied population. Another study investigated the prevalence of cell surface anti-neuronal antibodies in serum and CSF in new-onset psychoses compared to a control group. The study found that the occurrence of cell surface autoantibodies in new-onset psychoses is not more frequent compared to the control group, and if the antibody appears in the serum, the presence of the same antibody in the cerebrospinal fluid is not certain. Therefore, routine examination of these antibodies is not necessary during new-onset psychosis.

Onconeural antibodies have been hypothesized to contribute to immunological changes in psychiatric patients, but the literature on these antibodies in psychiatric disorders is scarce. Anti-Hu and anti-Yo antibodies were shown to induce neuronal and Purkinje cell death in hippocampal and cerebellar regions of rats. According to case reports, anti-Yo and anti-Ri onconeural antibodies may play a role in autoimmune processes in psychiatric patients. Only one patient was positive for anti-Amp antibody, two patients had borderline anti-Rec, and four patients had borderline anti-Yo, anti-Hu, anti-SOX1 or anti-Tr antibodies. Among our patients onconeural antibodies appeared more frequently (31.81%) than cell surface antibodies (4.54%).

No significant correlation was found between anti-neuronal antibodies and the PANSS scores of the examined patients. This result suggests that anti-neuronal antibodies do not influence the severity of psychosis induced by SCRAs. Previous studies have identified atypical dopamine activity in cannabis users, this mechanism that may underlie SCRA-induced psychosis.

In our previous studies, we detected natural autoantibodies against CS in healthy individuals and patients with autoimmune diseases. Natural IgM autoantibodies are polyreactive, recognize evolutionarily conserved self-structures, and serve as binding agents for damaged molecules and cells. They participate in the removal of apoptotic cells and maintain tissue homeostasis, therefore they play a role in the regulation of inflammation and immunological balance. The majority of natural autoantibodies were originally thought to be of the IgM isotype, but later the presence of natural IgG autoantibodies was also described, and their presence may be the result of an adaptive immune response. In pathological conditions, a compensatory increase of IgG antibodies with anti-idiotypic activity can occur, and we previously found elevated anti-CS IgG antibody levels in patients with systemic lupus erythematosus who were positive for anti-dsDNA IgG. In another study, in another autoimmune disease, significantly higher anti-CS IgG values were found in the active phase of diffuse cutaneous scleroderma compared to patients in the inactive phase and the control group. The presence of natural antibodies among central nervous system autoimmune diseases was investigated. It has been shown that anti-CS IgG is elevated in myasthenia gravis and Devic's disease, if the anti-Chlamydia IgG antibody is positive among these patients, which can be proven to play a role in the etiology of these diseases. This supports the participation of these antibodies in the adaptive immune response and autoimmunity. Consequently, a higher trend of anti-CS IgG levels, which resulted in a decrease in the ratio of anti-CS IgM/IgG autoantibodies in patients with anti-neuronal autoantibody positive/borderline results, may be a harbinger of autoimmune phenomena.

Another interesting and significant result of our study is that the anti-CS IgM/IgG ratio showed a negative correlation with PANSS positive symptoms. Thus, patients with positive psychotic symptoms, such as delusions and hallucinations, had elevated anti-CS IgG. This result raises the possibility of the idea that in the case of the appearance of positive psychotic symptoms, the occurrence of autoimmune processes in the background of the disease may be more typical. Further studies are needed to confirm this hypothesis.

Overall, we can conclude that the presence of anti-neuronal autoantibodies in the serum samples of acutely hospitalized patients with SCRA-induced psychosis is not exceptional. However, in most cases, routine antibody screening is probably not necessary in the case of SCRA-induced acute psychosis, because the occurrence of antibodies is not significantly related to the severity of psychosis, the duration of drug use, or the synthetic drugs the patient previously consumed. Further tests are needed to check the presence of antibodies in the cerebrospinal fluid, because according to a psychiatric study, the appearance of antibodies can be different compared to those in the serum.

To our knowledge, this is the first study to address the prevalence of anti-neuronal and natural autoantibodies in SCRA users. Previous studies have looked at the presence of anti-neuronal antibodies in patients treated for new-onset psychosis and other psychiatric illnesses, and found no significant correlation between the presence of autoantibodies and psychosis.

The use of synthetic drugs, including specifically the tested SCRA, can trigger autoimmune processes through a molecular mimicry mechanism, or it can stimulate B-lymphocyte cells to produce immunoglobulin by excessive stimulation of CB receptors. In the case of a damaged blood-brain barrier, immunoglobulins produced in the periphery also enter the central nervous system. We were able to significantly confirm the activity of the immune system at the level of natural antibodies with the decreased anti-CS IgM/IgG ratio in the anti-neuronal antibody positive cases. The presence of anti-neuronal antibodies was not associated with the severity of psychosis. In case of higher PANSS positive values, the anti-CS IgM/IgG ratio was significantly lower. This result raises the interesting question of whether, in the case of more dominant positive psychotic symptoms (hallucinations, delusions, persecutory thoughts), autoimmune processes are more prominent in the background of the disease. Further studies are needed to confirm this assumption.

6. Summary

I. Based on our case report, it was suggested that SCRA may be present as an epitope in the immune system and participate in the etiology of autoimmune encephalitis based on its molecular mimicry mechanism.

II. To our knowledge, our case is the first in which the combined role of autoimmune encephalitis and SCRA in the etiology of new-onset psychosis has been suggested.

III. In the case of drug-induced psychosis following SCRA use, the appearance of anti-neuronal autoantibodies in the serum is not significant, so their examination is not routinely necessary.

IV. The presence of anti-neuronal autoantibodies did not show a significant correlation with the severity of psychosis, the time of substance use and the multiple drug use.

V. Our study is, to my knowledge, the first study that examines the occurrence of anti-neuronal antibodies and natural antibodies in SCRA-induced psychosis.

VI. The presence of natural autoantibodies, especially an elevated anti-CS IgG level, suggests the occurrence of an underlying autoimmune disease. Therefore, the significantly low anti-CS IgM/IgG ratio in patients with positive and borderline antineuronal antibodies may indicate autoimmunity.

VII. The presence of natural autoantibodies shows a significant correlation with PANSS positive values. The anti-CS IgM/IgG quotient is low in patients with positive psychotic symptoms, which raises the possibility of autoimmunity in patients with delusions, hallucinations and persecutory thoughts.

7. List of own publications

7.1. Publications related to thesis

Cumulative impact factor: 5,435

1. **L. Hau**, T. Tényi, N. László, M. Á. Kovács, Sz. Erdő-Bonyár, Zs. Csizmadia, T. Berki, D. Simon, Gy. Csábi**: Anti-neuronal autoantibodies (cell surface and onconeuronal) and their association with natural autoantibodies in synthetic cannabinoid induced psychosis.** Frontiers in Psychiatry, (1664-0640 1664-0640) (2022) **IF: 5,435**

2. **L. Hau**, Gy. Csábi, B. Rózsai, J. Stankovics, T. Tényi, K. Hollódy: **Anti-N-methyl-D-aspartate receptor encephalitis and drug abuse - the probable role of molecular mimicry or the overstimulation of CB receptors in a 17-year-old adolescent - case report**. Neuropsychopharmacologica Hungarica 2016 Sep;18(3):162-16 (2016)

3. **L. Hau**, Gy. Csábi, T. Tényi: **Anti-N-metil-D-aszpartát-receptor encephalitis-útmutató a diagnosztikus és terápiás kihívásokhoz.** Psychiatria Hungarica 2015, 30 (4):402-408

4. **L. Hau**, Gy. Csábi, T. Tényi: **Anti-N-metil-D-aszpartát-receptor-encephalitis.** A hon- és rendvédelmi egészségügyi dolgozók VII. tudományos-szakmai konferenciája, Budapest: Dialóg Campus Kiadó, pp 61-70 (2019)

5. **L. Hau**, T. Tényi, N. László, M. Á. Kovács, Sz. Bonyár-Erdő, Zs. Csizmadia, T. Berki, D. Simon, Gy. Csábi: **Anti-neuronal autoantibodies (cell surface and onconeural) and their association with natural autoantibodies in synthetic cannabinoid-induced psychosis**. In: Guloksuz, S., Kirli, U., Elbi, H., eds. Substance Use and the Psychosis Spectrum. Lausanne: Frontiers Media SA. doi: 10.3389/ fpsyt.2022.850955 (2022)

7.2. Publications not related to thesis

Cumulative impact factor: 20,102

1. **L. Hau**, K. Kállay, G. Kertész, V. Goda, Cs. Kassa, O. Horváth, Z. Liptai, T. Constantin, G. Kriván: **Allogeneic haematopoietic stem cell transplantation in a refractory case of neuromyelitis optica spectrum disorder**. Multiple Sclerosis and Related Disorders, (2211-0348 2211-0356): 42 Paper 102110. 3 p. (2020) **IF: 4,339**

2. G. Horváth, R. Brubel, K. Kovács, D. Reglődi, B. Opper, A. Ferencz, P. Szakály, E. László, **L. Hau,** P. Kiss, A. Tamás, B. Rácz: **Effects of PACAP on oxidative stress-induced cell death in primary rat kidney and human hepatocyte cell cultures.** Molecular Neuroscience. JOMN-509R2 (2011) **IF: 2,922**

3. G. Horváth, B. Rácz, P.Szakály, P. Kiss, E. László, **L. Hau**, A. Tamás, Z. Helyes, A. Lubics, H. Hashimoto, A. Baba, D. Reglődi: **Mice deficient in neuropeptide PACAP demonstrate increased sensitivity to in vitro kidney hypoxia.** Transplantation Proceeding. 31.05.2010 Art:21904 (2010) **IF: 0,993**

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8. Acknowledgement

First of all, I would like to express my gratitude to my supervisor, Prof. Dr. Györgyi Csábi and my program leader, Prof. Dr. Tamás Tényi, who made it possible for me to work at the Pediatric Clinic and the Psychiatry and Psychotherapy Clinic of the University of Pécs Clinical Center and for supporting me troughout.

I would like to thank university assistant professor Dr. Simon Diána, who helped my work with a high level of professional competence and led the laboratory background and investigations of my work within the framework of the Institute of Immunology and Biotechnology.

I would like to thank Dr. Natália László and Dr. Áron Márton Kovács for their help, who helped in the collection of patients at the clinics and participated in the sampling.

I would like to thank Szabina Erdő-Bonyár and all the employees of the Institute of Immunology and Biotechnology for their tireless work, who provided help in statistics and material processing.

I owe special thanks to Prof. Dr. Tímea Berki, with whose permission and support I was able to perform the laboratory tests at the Institute of Immunology and Biotechnology as part of my clinical research.

I would also like to thank Prof. Dr. Dénes Molnár and Prof. Dr. Tamás Decsi for supporting me during my work as an employee of the PTE KK Pediatric Clinic.

I owe a debt of gratitude to my supervisor, Prof. Dr. Gergely Kriván and my colleagues, Dr. Krisztián Kállay, Dr. Gabriella Kertész, Dr. Csaba Kassa, Dr. Vera Goda, Dr. Katalin Csordás, Dr. Máté Horváth and the others who, with self-sacrificing work, they supported me throughout the completion of the PhD work with motivation and professional competence.

I would like to thank all the lovely employees of the Pediatric Clinic and the Psychiatric and Psychotherapy Clinic for the help I received during my work.

Last but not least, I would like to thank my family for their support and time, without whom this work would not have been possible. First of all, to my main support and help, my husband, Péter Laufer and my children, Soma and Sára, who fill my days with smiles. Also, to my Mom and Dad for giving me the time to work on my job and to all my other family members for believing in me, loving me and supporting me. I am thankful!