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

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Anti-N-methyl-D-aspartate encephalitis is an autoimmune disorder characterized by autoantibodies produced against NMDA receptors. We report the case of a 17-year-old drug user teenager who presented with altered mental scale, psychiatric symptoms and autonomic dysfunction. In the background we diagnosed NMDA encephalitis. We supposed that synthetic cannabinoids/drugs may have lead to the of trigger NMDA encephalitis via the altered activation of the immune system and molecular mimicry mechanism.

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Keywords: anti-n-methyl-d-aspartate encephalitis, synthtetic drugs, mimicri, autoimmune disorder

Among young adults synthetic drug use is widespread. In Hungary 68% of drug users used synthetic psychostimulants in 2014. The relationship between substance use disorder and encephalitis was not examined before in detail. Anti-N-methyl-D-aspartate (NMDA) encephalitis is an autoimmune disorder characterized by autoantibodies produced against NMDA receptors. The disease had been first described in 2005 by cases of ovarian teratomas (Dalmau et al., 2007). However, it could occur in all ages, and most reported cases point to the incidence of NMDA encephalitis in teenagers and young adults, mostly in females. Viral agents and teratoma can be in the background due to a molecular mimicry in the central nervous system. During the progression of the disease prodromal flu-like symptoms, psychiatric manifestations and neurological symptoms appear. For the diagnostic evaluation EEG shows an atypical generalized slow pattern, and MRI scans often show no special findings. Oligoclonal gammopathy in the cerebrospinal fluid is a nonspecific marker, while anti-NMDR antibodies in the CSF and the serum indicate the presence of anti-NMDA receptor encephalitis (Dalmau et al., 2008). Here we report a case of NMDA encephalitis in a 17-year-old boy with the history of drug abuse and emphasize the differential diagnostic challenge.

CASE REPORT

A 17-year-old previously healthy teenager was admitted at the Traumatology Department after an uncertain head injury. He did not remember what happened to him, and seemed to be intoxicated. It was prominent from his psychiatric history that he was a drug user, especially abusing synthetic cannabinoids. During the traumatologist attendance a tonic-clonic seizure occurred, which was treated by intravenous benzodiazepine. CT scan was performed which was negative. After the first evaluation, regarding the seizure he was sent to the neurology ward of the Department of Pediatrics. His neurological examination was negative. Toxicology test was positive for cannabinoids and benzodiazepines (which could be caused by the benzodiazepine therapy). We performed a negative EEG test. Considering cooperation problems (escaping from our department), the normal EEG and the not repeated seizure his condition was regarded as an occasional seizure and the patient was discharged. On the same day he was rehospitalized

because of a second tonic-clonic seizure. During the following days his behavior deteriorated, he started to walk naked, became aggressive and had acoustic and visual hallucinations. During the observation period his psychomotility started to change, catatonia signs like stupor and mutismus developed. After one week his consciousness deteriorated, he had more frequent and serious seizures and intensive care was required. Repeated EEG examination showed generalized slowing. Acute intracranial MRI was normal. The biochemical, microbiological and native cerebral fluid examination was negative. Oligoclonal gammopathy had been shown from the cerebral fluid, and while the autoimmune encephalitis panel had been examined by indirect immunofluorescence test from the cerebral fluid and serum, antibodies against NMDA receptors had been revealed. He had been treated with high-dose steroids (1g/day) for five days, but his condition did not change. Therefore, we performed plasma exchange five times. After plasma exchange his condition improved, symptoms disappeared. After the acute intensive period he had taken low dose steroids for a month and antipsychotic drugs (risperidone 1,5 mg/day) and benzodiazepines (clonazepam 3 mg/day) for a long time. He was at our department for 2 months and we discharged him without any symptoms. For 6 months he had not been admitted to the hospital, he was controlled at the outpatient care unit. After that he started to discontinue his antipsychotic medications and restarted the used illicit drugs, and seizures appeared again. During his further admissions to the emergency department he was acting aggressively and escaped before laboratory tests. Repeated drug test was negative for classical drugs, but the teenager told us about his synthetic cannabinoid use. Because of compliance problems we could not check antibody levels again. The history of illicit drug use and the probable role of molecular mimicry mechanism suggest a connection between synthetic drug use and anti-NMDAR encephalitis, but further examinations and case reports are needed to confirm this hypothesis.

DISCUSSION

Our case represents a differential diagnostic challenge of anti-NMDAR encephalitis. Illicit substance use can often lead our thinking toward the direction that symptoms are caused by drugs or even a withdrawal mechanism. Tonic-clonic seizure can be induced by drug abuse with an endogenous susceptibility. Even a psychosis can be resulted by illicit drug abuse, which symptoms had shown in this case (visual, acoustic hallucinations). However, it is important to not concentrate only on one anamnestic point to set up correct diagnosis. As we mentioned before, viral agents and tumors can cause autoimmune encephalitis, and our hypothesis is that a synthetic illicit drug can also be an epitope of the immune system which can lead to an overproduction of immunoglobulins against the central nervous system. In our case a head injury or drug use could have caused disruption in blood brain barrier and the circulating immunoglobulins could enter the central nervous system. Several studies had shown that cannabinoids have immunomodulatory effect via CB1 and CB2 receptors (Jean-Gilles et al., 2010,Tanasescu, Constantinescu, 2010). CB1 receptors mostly occur in the central nervous system and regulate synaptic transmission and thus mediate psychoactive effects (Croxford, 2003). CB2 receptors were initially found on periphery, particularly in immune cells (macrophages and B cells) but seem to play an important role in the central nervous system immune mechanisms (Tanasescu, Constantinescu, 2010). The production of endocannabinoids regulates various cells of the immune system. During inflammation microglia, astrocytes, macrophages and neurons produce high levels of endocannabinoids which bind to CB receptors and attenuate neuronal damage. The synthetic cannabinoids can cause an overstimulation or unexpected effect on CB receptors. This unexpected CB stimulation probably produces an excitatory impact on the immune system which can lead to autoimmune encephalitis due to the overstimulation of plasma cells.

Differential diagnostic difficulties should not mislead our thinking, even if the person is an illicit drug user. We hypothesize that synthetic cannabinoid use can be in the background of autoimmune encephalitis even with a mimicry mechanism or overstimulation of CB receptors, however, to prove this, further examinations and case reports will be necessary.

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Anti-N-metil-D-aszpartát receptor enkefalitisz és droghasználat – a molekuláris mimikri vagy a CB receptorok túlstimulálásának lehetséges szerepe

Anti-N-metil-D-aszpartát enkefalitisz autoimmun betegség, ahol az NMDA receptorok ellen termelődnek autoantitestek. Esetismertetésünk során egy olyan 17 éves szerhasználó fiatal esetét mutatjuk be, ahol a tudatzavar, pszichiátriai tünetek és autonóm diszfunkció hátterében NMDA enkefalitisz igazolódott. Hipotézisünk során azt feltételezzük, hogy a szintetikus drogok a szervezetben molekuláris mimikri mechanizmusával az immunrendszer kóros működéséhez vezethetnek, mely folyamatok az NMDA enkefalitisz etiológiájában szerepet játszhatnak.

Kulcsszavak: Anti-N-metil-D-aszpartát enkefalitisz, szintetikus drogok, mimikri, autoimmun betegség