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Research Article

Cannabidiol for Treatment Epilepsy and Russian Experience

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Abstract

Cannabis is known as medical plant and also psychoactive drug by numerous civilizations for millennia. Currently, cannabidiol (CBD) is successfully used for the treatment of epilepsy, especially pharmacoresistant forms. We presented 11 personal observation of epileptic patients on CBD therapy, 10 of them previously demonstrated pharmacoresistance. The positive effect of CBD was noted in 7 (63,6%) from 11 patients - four patients with > 50% decrease in seizures, one with > 75% decrease, one girl developed clinical remission of seizures (but with preservation of epileptiform discharges on the EEG) and one boy without seizures with reduction of the ESES pattern. Positive effect demonstrated genetic cases of Dravet syndrome, mental retardation X-linked 98 with Lennox-Gastaut phenotype, child with MACF1 mutation, epileptic girl with Down syndrome and three cases of epilepsy in cerebral palsy patients. In only 4 pharmacoresistant patients (36,4%) no objective improvement was revealed. No negative somatic and behavior side effects of the CBD were observed. So cannabidiol treatment can be regarded as a safe and effective method of treating epilepsy.

Keywords: *Cannabidiol; CBD; Pharmacoresistant Epilepsy; Epileptic Encephalopathy*

Introduction

Cannabis sativa is one of the first plants domesticated by mankind and cannabis has been used as medicine by numerous civilizations for millennia as evidenced not only by written sources, but also by objective paleobotanical studies [1]. Ancient Egyptian, Mesopotamian, Chinese and Indian manuscripts mentioned cannabis as a medical plant and also psychoactive drug [2-4].

Cuneiform clay tablets of ancient Sumerian and Akkadian (XXIV-XXIII century BC) texts mention the use of cannabis for the treatment of nocturnal convulsions. The Greek and Roman doctors Pedanius Dioscorides (~40 - 90 AD) and Claudius Galen (129 - 216 AD) described numerous medical indications for the use of cannabis, including rheumatic pains, constipation, malaria, disorders of the reproductive system in women, headaches and convulsions [5].

In Arabic manuscripts of the VIII-XI centuries AD, cannabis was used as an analgesic, anti-inflammatory, anthelmintic, diuretic drug and also for the treatment of epilepsy [6].

Thanks to the works of famous Irish and British doctor and scientist Sir William Brooke O'Shaughnessy (1809 - 1889), the long-standing experience of Oriental medicine became known to Western specialists. In 1839 "Case of tetanus, cured by a preparation of the cannabis indica" was published [7]. In 1842, the book "Bengal Pharmacopoeia" was written, describing in detail the medical use of Indian cannabis preparations [8] and in 1856 W.B. O'Shaughnessy was knighted by Queen Victoria for his works.

Phytocannabinoid cannabidiol (CBD) was isolated and identified from Cannabis sativa in 1940 [9] and the most psychoactive tetrahydrocannabinol (THC) was isolated and its structure elucidated by synthesis in 1964 [10].

For a long time, the fear of the spread of marijuana addiction was an obstacle to the use of cannabinoids in medicine. However, in 2018 the cannabidiol drug Epidiolex was approved by the Food and Drug Administration in the United States for the treatment of two epilepsy disorders - Lennox-Gastaut and Dravet syndromes [11]. At present, clinical research on CBD included studies related to anxiety and depression, cognition, movement disorders, epilepsy and pain. Currently, most international antiepileptic conferences contain sessions dedicated to the problems and the success of CBD in the treatment of epilepsy.

Materials and Methods

At the period of 2019-2022 11 epileptic patients (10 pediatric and one adult, 8 males and 3 girls, age from 2,5 up 21 years) treated with cannabidiol were observed on the Neurology, Neurosurgery and Medical Genetics Department, Pirogov Russian National Research Medical University. Clinical, anamnesis and laboratory data were analyzed. Dynamical video-EEG monitoring investigations were performed by "Encephalan-Video" RM-19/26 (Medicom MTD, Russia) and "NeuroScope'' NS432, NS25A, NS450A (Biola, Russia). Magnetic resonance visualization had obtained for all the patients (Siemens Magnetom Aera 1,5 Tl, Germany, Signa Infinity 1,5 Tl General Electric, USA). DNA sequencing was obtained (Next Generation Sequencing on platform Illumina NextSeq 500, USA, Illumina HiSeq 1500, USA and Illumina NovaSeq 6000, USA).

Results

The analyzed population was dominated by boys (n = 8, 72,7%). Median age of patients was 8,64 ± 5,92 varied from 2,5 up 21 years. Most of the patients (n = 10, 90,9%) had clinical epileptic seizures of various types (including those objectively recorded on dynamic video EEG monitoring) and only one child with cerebral palsy had convulsive epileptic encephalopathy (cognitive epileptiform disintegration) with ESES, which significantly complicated the implementation of habilitation measures. All the patients are presented at table 1.

In the structure of etiological factors, a serious proportion of genetic cases (n = 5, 45,5%) draws attention, including three cases of gene mutations, a chromosomal anomaly (Down syndrome) and deletion syndrome of genomic imprinting (Angelman syndrome). Other cases (n = 5, 45,5%) had severe perinatal pathology with the formation of cerebral palsy with the exception of one girl with cryptogenic case, the genetic etiology of whose condition is highly probable, but whole genome study did not reveal any violations.

The eldest patient is young male N. 21-years-old with clinical characteristics of epileptic encephalopathy with mental retardation who had newly identified de novo microdeletion in KIAA2022 gene. Previously not described variant - chromosome X: g.73962680_73962683del ENST00000055682.6: c.1713_1716del ENSP00000055682.5: p.Ser571ArgfsTer13 in result of microdeletion of four nucleotides caused reading frame shift error with and loss of function in KIAA2022 (NEXMIF) gene. Russian case of X-linked mental retardation-98 with epileptic encephalopathy, mental retardation and atypical autism with positive experience of CBD treatment was published in 2020. Epileptic syndrome considered as the case of late-onset cryptogenic spasms with later developing of Lennox-Gastaut-like phenotype and variant of severe epilepsy with multifocal independent spike-wave foci syndrome (SE-MISF) [12].

One boy had severe course of Dravet syndrome with identified sodium channelopathy - SCN1A gene mutation (chr2:g.166909379G>A ENST00000303395.4: c.677C>T ENSP00000303540.4: p.Thr226Met).

In 6 year old boy with cerebral palsy and pharmacoresistant epilepsy - Markand-Blume-Ohtahara syndrome (SE-MISF – severe epilepsy with multifocal independent spike-wave foci) was found mutation of MACF1 gene (chr1:g.39847823A>G ENST00000545844.1: c.7661A>G ENSP00000439537.1: p.Gln2554Arg). Mutation of MACF1 gene responsible for the formation of lissencephaly 9 with complex brainstem malformation (OMIM#618325). But the boy had no lissencephaly or pachygyria but had gross post-ischemic multicystic transformation of the cerebral hemispheres on magnetic resonance imaging.

The vast majority of the examined patients (n = 10, 90,9%) had a negative experience of pharmacoresistance to AEDs, including 7 cases of aggravation to various drugs (lamotrigine, levetiracetam, carbamazepine and oxcarbazepine, topiramate, etc). And only one girl with Down syndrome received CBD as an initial treatment, since her mother was very negative about anticonvulsants due to the risk of negative effects, which she had read and heard about.

The positive effect of CBD was noted in 7 (63,6%) from 11 patients - four patients with > 50% decrease in seizures, one with >75% decrease, a girl on CBD monotherapy with clinical remission of seizures (but with preservation of epileptiform discharges on the EEG) and one boy without seizures with reduction of the ESES pattern (Figure 1 and 2).

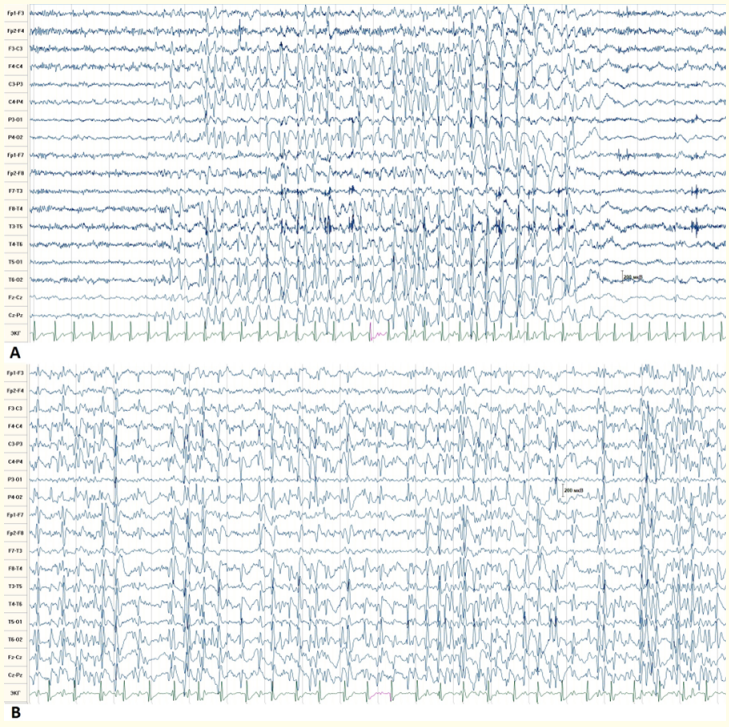

Figure 1: *Patient S.S. at 7,5 years old. EEG before CBD treatment.*

A: Wake EEG - diffuse spreading of BEDOC-like epileptiform complexes with right temporo-central accentuation.

B: Sleep EEG demonstrates ESES with accentuation of diffuse epileptiform discharges in temporo-parieto-central regions of right hemisphere.

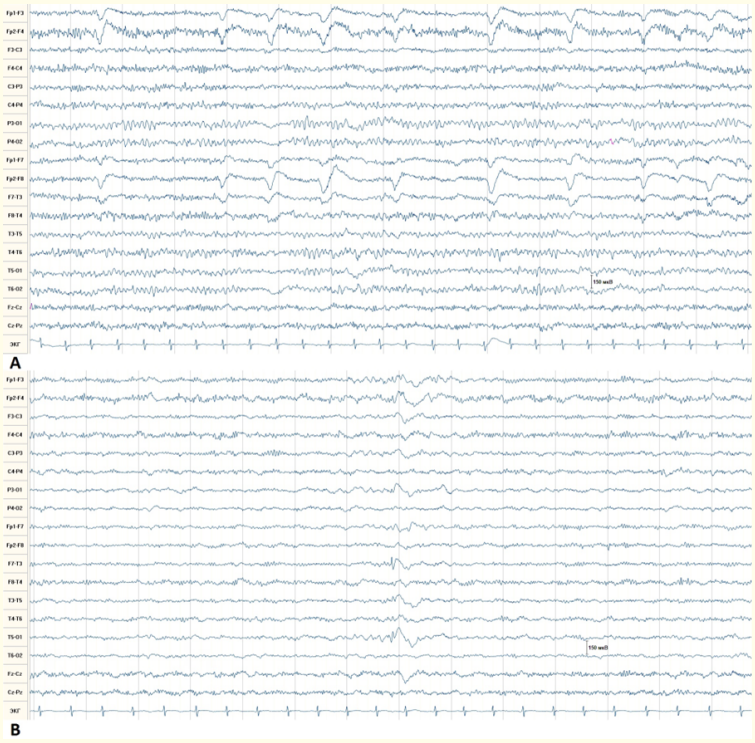

Figure 2: *Patient S.S. at 9 years old. EEG on CBD treatment (started 3 months ago).*

A: Wake EEG demonstrates blocking of epileptiform discharges and formation of physiological alpha rhythm.

B: Sleep EEG - the reduction of the ESES pattern with the presence of rare peak waves accentuated in the left temporal region of the low index.

In 4 patients (36,4%), no objective improvement was revealed. But should be noted that the mother of one child with no effect of CBD on seizures and epileptiform discharges on the EEG continues to give this drug for the child, due to the improvement of the somatic condition (increased appetites, good bowel movement), positive mood and emotional reactions.

None of the parents of our patients complained about the negative somatic and behavior side effects of the CBD.

Unfortunately, cannabidiol is not registered and has not been approved in Russia. Parents have to bring CBD from abroad on their own risk. Our patients received 8% and 10% cannabidiol in doses varies 0,2 - 1 mg per kilo. Despite the recommended twice daily intake of medication, our experience shows better effect of distributing the daily dose into three reception times.

Discussion

The mechanisms of action of cannabinoids in epilepsy have not yet been sufficiently studied. Nevertheless, it has long been known that endocannabinoid system is the critical regulator of synaptic inhibition in brain and was supposed to be closely involved in epilepsy. Cannabinoid receptor are mostly located on the presynaptic terminals of both excitatory and inhibitory neurons, but with characteristic distribution varying in different brain areas and synapses [13].

The principal active component of marijuana is the cannabinoid Δ9-tetrahydrocannabinol (THC) which could be also pro- and anticonvulsant; but cannabinol is another cannabinoid which has positive effect of preventing and in reducing seizures [14].

In 2014 Gloss D and Vickrey B summarized the experience of trial reports that included a total of 48 patients in which cannabidiol was used as the treatment agent [15].

In 2015 Dimah Saade and Charuta Joshi from Division of Pediatric Neurology, University of Iowa Children's Hospital demonstrated successful experience of pure cannabidiol in the treatment of malignant migrating partial seizures in infancy in 10-month-old boy with sustained seizure reduction [16].

In 2018 US Food and Drug Administration approval of a purified cannabidiol extract for the treatment of two highly refractory pediatric epilepsy syndromes - Dravet and Lennox-Gastaut, what gave the hope to patients and their parents for stable and safe seizure control [17].

This event was preceded in particular with the completion of randomised, double-blind, placebo-controlled phase 3 trial of cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE3 and GWPCARE4 studies). Patients received plant-derived pharmaceutical formulation of highly purified CBD (Epidiolex, 100 mg/ml oral solution) at 10 mg/kg/day or 20 mg/kg/day or placebo for 14 weeks. Treatment started at 2.5 mg/kg/day for all groups and reached 10 mg/kg/day on day 7. Randomly assigned 171 patients to receive cannabidiol (n = 86) or placebo (n = 85). 14 patients in the cannabidiol group and one in the placebo group discontinued study treatment; all randomly assigned patients received at least one dose of study treatment and had post-baseline efficacy data. The median percentage reduction in monthly drop seizure frequency from baseline was 43,9% (IQR -69,6 to -1,9) in the cannabidiol group and 21,8% (IQR -45,7 to 1,7) in the placebo group. So, cannabidiol demonstrated efficacious for the treatment of patients with drop seizures associated with Lennox-Gastaut syndrome and generally was well tolerated [18,19].

Also, two randomized controlled trials, GWPCARE1 (NCT02091375) and GWPCARE2 (NCT02224703) demonstrated efficiency and safety of CBD treatment in patients with Dravet syndrome [20]. Changqing Xu., *et al*. (2021) make a conclusion about the neuroprotective effects of cannabidiol in patients with Dravet syndrome [21].

Dale T., *et al*. (2019) evidenced of successful application experience of CBD for severe pediatric epilepsies such as CDKL5 deficiency disorder caused developmental and epileptic encephalopathy type 2 with the early-onset and refractory nature of the seizures. Also, authors emphasize that cannabis based products have attracted significant attention over recent years, driven by reports of miraculous cures of severe cases and a renewed public preference for "natural" therapies, thus placing intense pressure on both - the health professionals and the government for regulatory change [22].

In March 2022 German neurologists from Charité-Universitätsmedizin Berlin reported about 3 patients (age 8, 13 and 14 years) with positive effect of cannabidiol in addition to their current antiseizure medication in drug-resistant epilepsy due to Rasmussen encephalitis [23].

At present time the data of systematic reviews and meta-analyses shows, that there are enough positive research results in the world that indicate the validity of the medical use of cannabinoids. At the same time, experimental and clinical work is needed to further study their mechanisms of action, features of pharmacokinetics and pharmacodynamics, their effectiveness and safety in many severe and disabling diseases, such as also pharmacoresistant forms of epilepsy [24].

Conclusion

Numerous international studies show the effectiveness and safety of the use of cannabinoids in treatment of epilepsy, including severe forms. Our personal observations also confirm this statement. CBD can help in the curation of such epileptic encephalopathies as Dravet, Lennox-Gastaut syndromes and epilepsy with ESES. Also, CBD is drug of choice for patients and its relatives experiencing fear of side effects and the aggravation potential of anticonvulsants. In addition, would like to remind that the children with epileptic encephalopathies, delay of psychomotor and speech development and autistic behavior need a comprehensive examination, including video EEG monitoring, good quality neuroimaging and mandatory genetic examination by new generation exome sequencing techniques. Genetic verified cases with high risk of paradoxical effect of AEDs are good candidates for CBD therapy. So, cannabidiol treatment could be helpful for therapy of pharmacoresistant epileptic encephalopathies and could improve the quality of life for patients and their relatives.

Conflict of Interest

The authors declare that there is no conflict of interest.

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