BRIEF REPORT

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Brief Report: Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems—A Retrospective Feasibility Study

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Abstract

Anecdotal evidence of successful cannabis treatment in autism spectrum disorder (ASD) are accumulating but clinical studies are lacking. This retrospective study assessed tolerability and efficacy of cannabidiol-rich cannabis, in 60 children with ASD and severe behavioral problems (age = 11.8 ± 3.5, range 5.0–17.5; 77% low functioning; 83% boys). Efficacy was assessed using the Caregiver Global Impression of Change scale. Adverse events included sleep disturbances (14%) irritability (9%) and loss of appetite (9%). One girl who used higher tetrahydrocannabinol had a transient serious psychotic event which required treatment with an antipsychotic. Following the cannabis treatment, behavioral outbreaks were much improved or very much improved in 61% of patients. This preliminary study supports feasibility of CBD-based cannabis trials in children with ASD.

Keywords Cannabidiol · Medical cannabis · Medical marijuana · Autism spectrum disorder · Disruptive behavior

Introduction

About 50% of children with autism spectrum disorder (ASD) suffer from behavioral problems such as tantrums, self-injury and violence (Maskey et al. 2013). These behavioral difficulties increase their social isolation, limit their ability to benefit from intervention efforts and often cause more distress to caregivers than the core autistic symptoms. Unfortunately, about 40% of children with ASD and disruptive behavior do not respond well to standard behavioral and medical treatment (Adler et al. 2015). Consequently, an exceptionally high percentage of parents are seeking help through unproven methods (Hofer et al. 2017), including the use of compounds made of the cannabis plant.

The cannabis plant contains two main cannabinoids: tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is psychoactive and can cause anxiety and psychosis. CBD is not psychoactive and has potential anxiolytic, antipsychotic, anti-inflammatory and antioxidant properties with a relatively high toxicity threshold (Campos et al. 2017). Recently, CBD is emerging as a therapeutic option for refractory epilepsy (Devinsky et al. 2017, 2018; Thiele et al. 2018) and a CBD compound (Epidiolex, GW pahrmaceuticals) was approved by the U.S. Food and Drug Administration to treat severe forms of epilepsy (Lennox Gastaut and Dravet syndromes). These findings are of specific importance for people with ASD, as 10–30% of people with ASD have comorbid epilepsy (Ballaban-Gil and Tuchman 2000) and several synaptic plasticity pathways appear to be involved in both disease processes (Lee et al. 2015).

Moreover, alerted activation of the endocannabinoid system (ECS) was found in various animal models of epilepsy (Rosenberg et al. 2017) and ASD (Zamberletti et al. 2017). In some of these models, activating of the ECS or administrating CBD (Kaplan et al. 2017; Gururajan et al. 2012) ameliorated the social deficits.

A recent study demonstrated reduced concentration of the endocannabinoid anandamide in children with ASD (Karhson et al. 2018). However, to our knowledge, there

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is no previous report on the impact of medical cannabis in children with ASD.

Methods

Patients

All children with ASD and refractory disruptive behaviors, in a single national referral center (Shaare Zedek Medical Center, Jerusalem, Israel), to whom medical approval to use cannabis was issued for this indication, between 4/2016 and 1/2017, were systematically investigated after 7–13 months of treatment (August 2017). Prior to the retrospective collection of data, written informed consent was obtained from parents of all children.

Treatment

The cannabis was given as an adjuvant therapy, upon parental request, following specific individual approval of the Israeli Ministry of Health. All children were prescribed whole plant extracts that contain CBD and THC in a 20:1 ratio, dissolved in olive oil (CHP, ™Better, Israel; Avidekel, Tikun Olam Ltd, Israel, Topaz BOL Pharma, Israel). The cannabis oil was given sublingual two to three times a day with doses up-titrated over 2–4 weeks, to effect and tolerability (starting CBD dose was 1 mg/kg/day, maximal CBD dose was 10 mg/kg/day).

Outcome Measures

Patients were assessed using the following questionnaires: a modified Liverpool Adverse Events Profile, the Caregiver Global Impression of Change (CGIC) scale, the Home Situations Questionnaire–Autism Spectrum Disorder (HSQ-ASD) and the Autism Parenting Stress Index (APSI). More details on the instruments and statistical analysis are described in the Supplementary Material.

Results

Patients

The sample consisted of 60 children, 5–18 years old. Mean age was 11.8 ± 3.5 years; 77% had low cognitive functioning based on preexisting psychological evaluations [Autism Diagnostic Observation Schedule (ADOS) or Childhood Autism Rating Scale (CARS)]; 83% were boys. Clinical

characteristics of the group are summarized in Table S1, available online.

All children attended special education programs for children with ASD and at the time of the treatment met DSM-5 criteria for ASD. All had severe behavioral problems, based on a Clinical Global Impression Scale—Severity (CGI-S) score of 6 or 7.

Treatment

The initial treatment for all patients was a whole plant extract that contains CBD and THC in a 20:1 ratio. In 29 patients with an insufficient response (CGI-S scores ≥ 5 despite treatment), strains with lower CBD:THC ratios were tried (up to a 6:1; maximal CBD dose was 5 mg/kg/day). The lower CBD:THC ratio was reported to be much better by parents of 13 patients, slightly better in 7 patients, no change in 6 and worse in 3. The mean total daily dose was 3.8 ± 2.6 mg/kg/day CBD and 0.29 ± 0.22 mg/kg/day THC for children who received three daily doses (n = 44) and 1.8 ± 1.6 mg/kg/day CBD and 0.22 ± 0.14 mg/kg/day THC for children who received two daily doses (n = 16).

Retention Rates

By the end of this study, forty-four children (73%) were still on cannabis treatment (mean treatment duration: 10.9 ± 2.3 months). Sixteen children (27%) stopped the cannabis treatment after 4.1 ± 2.6 months due to the following reasons: Three were treated for less than 2 weeks due to marked irritability in two and unsuccessful attempts to give the oil in the third. These 3 were excluded from the efficacy assessments below. Five children stopped the treatment (after 6 ± 2 months) due to low efficacy, seven (after 4.0 ± 2.1 months) due to a combination of low efficacy and side effects and one adolescent girl stopped the treatment after 6 months due to a transient psychotic event.

Adverse Events

Adverse events were reported by parents (n = 57) throughout the treatment period and were systematically assessed at each patient visit and at the end of the study (Table 1). Hypervigilance leading to aggravation of sleep problems was reported in 14% of the patients but usually resolved by omitting or adjusting the evening dose. Other common side effects included restlessness, irritability and loss of appetite. Three children (5%) stopped the treatment due to side effects that included marked irritability after treatment onset in 2 cases and a psychotic event in one adolescent girl. This 13 years old girl received 6.5 mg/kg/day CBD and no other

Table 1 Adverse events reported by parents during the treatment with cannabis

Adverse event	No of patients (%)
Any adverse event	29 (51%)
Sleep disturbances	8 (14%)
Restlessness	5 (9%)
Nervousness	5 (9%)
Loss of appetite	5 (9%)
Gastrointestinal symptoms	4 (7%)
Unexplained laugh	4 (7%)
Mood changes	3 (5%)
Fatigue	3 (5%)
Nocturnal enuresis	2 (3.5%)
Gain of appetite	2 (3.5%)
Weight loss	2 (3.5%)
Weight gain	2 (3.5%)
Dry mouth	2 (3.5%)
Tremor	2 (3.5%)
Sleepiness	1 (2%)
Anxiety	1 (2%)
Confusion	1 (2%)
Cough	1 (2%)
Serious adverse event	No of patients (%)
Psychotic event	1 (2%)

medications. She gradually increased the THC dose and when she reached 0.72 mg/kg/day, she developed an abrupt behavioral change that included unusual vocalization and refusal to eat and sleep for 48 h. She stopped the CBD and THC and started Ziprasidone 1.4 mg/kg/day. The symptoms resolved after 9 days.

Global Impression of Change in Behavior, Anxiety and Communication Following Cannabis Treatment

Figure 1 demonstrates the overall improvement in behavior, anxiety and communication as rated by parents on the CGIC scale. Considerable improvement in behavior problems ('much improved' or 'very much improved') was reported in 61% of the children. Considerable improvement in anxiety and communication problems was reported in 39% and 47% of the children respectively. CGIC ratings were not correlated with age, functional level, severity of behavioral problems at baseline and comorbidity with epilepsy.

Improvement in Disruptive Behavior Assessed by the HSQ-ASD and APSI

HSQ scores improved by 29% from 4.74 ± 1.82 at baseline to 3.36 ± 1.56 following the cannabis treatment. The mean improvement was 1.38 ± 1.79 (median $= 0.81$).

APSI scores improved by 33%, from 2.04 ± 0.77 at baseline to 1.37 ± 0.59 following the cannabis treatment. The mean improvement was 0.66 ± 0.74 (median $= 0.53$).

Concomitant Use of Medications

Forty nine children (82%) were treated with medications and cannabis concomitantly: 43 children (72%) used antipsychotics 10 (17%) received mood stabilizers, 7 (12%) received benzodiazepines, 4 (7%)—SSRIs and 4 (7%) received stimulants (details appear in the Supplementary Material, online). Following the cannabis treatment, 16 (33%) received fewer medications or lower dosage, 12 (24%) stopped taking medications and 4 (8%) received more medications or higher dose.

Discussion

To our knowledge, this is the first report on the impact of CBD-rich medical cannabis in children with ASD. Specifically, following the cannabis treatment, behavioral outbreaks were much improved or very much improved in 61% of patients. Moreover, 16 children (33%) received less medications or lower dosage and 12 (24%) stopped taking medications (all received at least 1 antipsychotic), while 4 children (8%) received more medications or higher dose. However, strains with a relatively high THC concentration (6:1-CBD to THC ratio) might lead to a serious psychotic episode that would require treatment with an antipsychotic.

Based on these promising results, we have launched a placebo controlled cross-over trial that will assess CBD-rich cannabis in 150 children with ASD and disruptive behavior (NCT02956226). Another large placebo controlled study (NCT03202303) will assess Cannabidivarin (CBDV), a homolog of CBD, in 100 children with ASD.

CBD-rich cannabis might help children with ASD via several possible mechanisms including its anxiolytic and antipsychotic properties (Campos et al. 2017) as well as its immunomodulatory effect and its impact on the endocannabinoid system (ECS). Several human studies revealed associations between polymorphisms in the gene encoding CB1 endocannabinoid receptor and social reward processing (Chakrabarti and Baron-Cohen 2011).

A Behavior

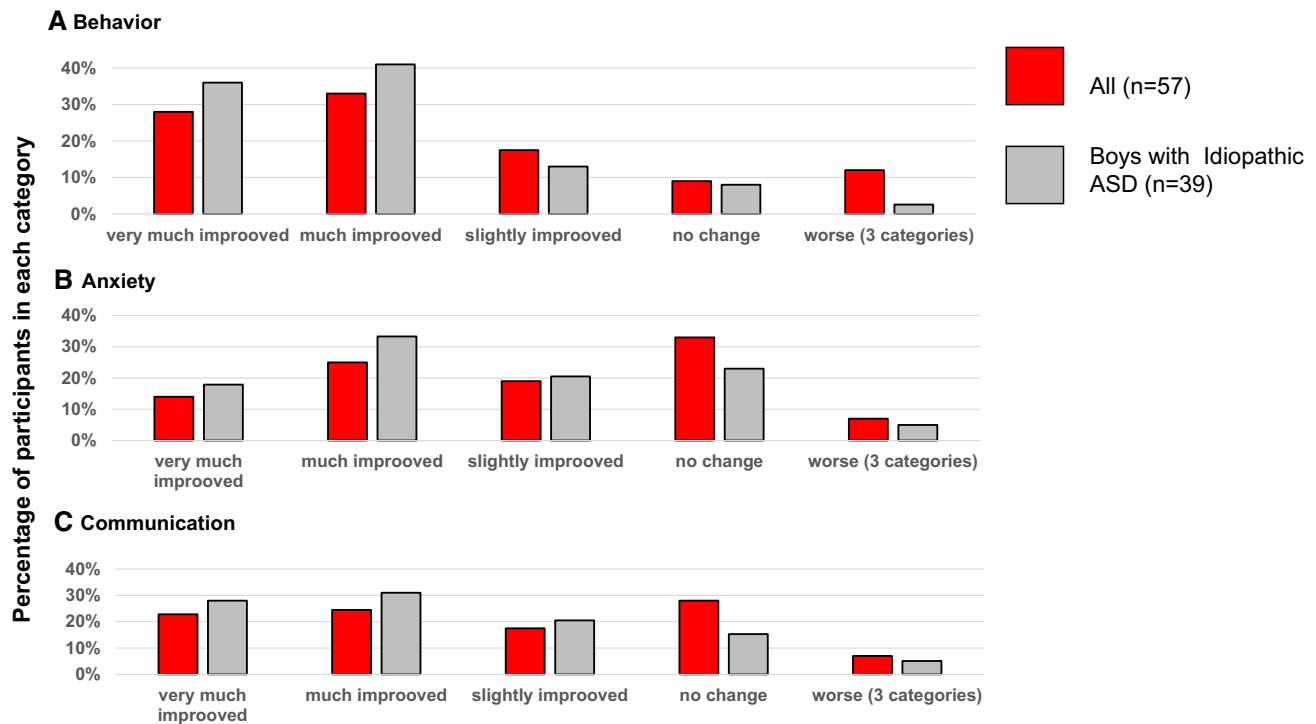**B** Anxiety

C Communication

Fig. 1 Caregivers global impression of change in behavior anxiety and communication following cannabis treatment

These preclinical data and the results of the current study render worthwhile further exploration of this treatment avenue in controlled studies. Until such evidence is available, physicians should be cautious in the use of medical cannabis in children with ASD since initial reports of promising treatment in children with ASD are often found, in controlled studies, to result from a pure placebo response (King et al. 2013). Furthermore, the use of recreational cannabis in adolescents is associated with several risks including decreased motivation, addiction, mild cognitive decline, and schizophrenia. However, these complications are all attributed to THC, while we used CBD-rich compounds. Nevertheless, as safety data in children are sparse, it is recommended that clinical use be withheld until ongoing randomized trials are published.

Finally, this study has several limitations. It is an uncontrolled retrospective study of a subgroup of children with severe and refractory behavioral problems. The participants used various cannabis strains from different growers and a broad range of CBD and THC dose, and the number of participants was not large enough to evaluate the impact on different ASD subgroups.

Author Contributions AA: Study conception and design; acquisition, analysis and interpretation of data; drafted manuscript; critically revised manuscript and gave final approval. CH and LA: Study conception; interpretation of data; critically revised manuscript and gave final approval. WN: Study design; acquisition of data; critically revised manuscript and gave final approval. EH: Study design; acquisition, analysis and interpretation of data; drafted manuscript; critically revised manuscript and gave final approval.

Compliance with Ethical Standards

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