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INTRODUCTION.

Regulation of cannabis in Chile is currently guided by Law number 20.000 (year 2005) and Health Ministry decrees (December, 2015), permitting self-cultivation for medical purposes (Figure 1). Daya Foundation has been the first organization in obtaining official permission for growing cannabis for medical research. Our Foundation also has provided medical support to many patients with different uncontrolled conditions. Refractory epilepsy is one of the neurological diseases that has been increasingly reported having a dramatically good response to the whole plant cannabinoids. The endocannabinoid system (Figures 2, 3) and their extensive modulation of many different neurotransmission processes is the most plausible hypothesis for these incredible results.



Figure 1. Current medicinal cannabis regulation around the world

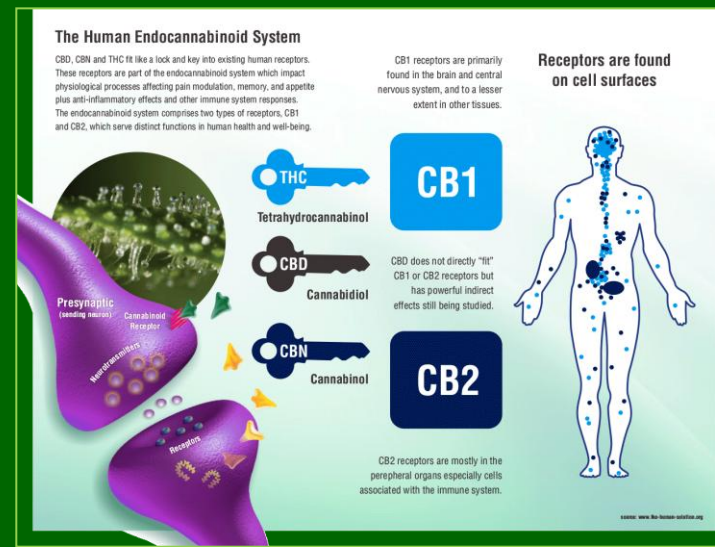


Figure 2. The endocannabinoid system

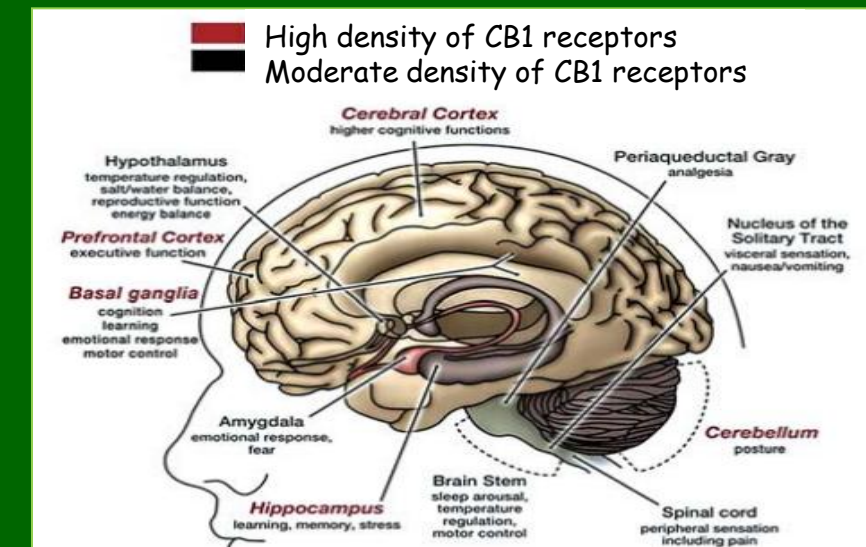


Figure 3. CB1 receptor density in the brain

PURPOSE.

To report our preliminary findings in a series of patients with different types of refractory epilepsy treated with oral cannabis extracts.

RESULTS.

Nine children and two adult patients were selected. Mean age: 11.5 yo (range: 1-37), six females. Etiologies are shown in Table 1. Mean follow-up was 14 mo. Seizure outcome is shown in Table 2. Three patients (27.3%) did not significantly improve or had seizure aggravation by high-CBD extracts. Adverse events included irritability (2 patients), insomnia (2 patients), and somnolence (1 patient) but they were easily solved by changing the dose or strain. Most parents/patients reported improvement in behavior, cognition, sleep, alertness, mood and/or motor function. Worse QOL items previous to treatment were scholar assistance, learning, and seizure frequency. The best outcome in QOL corresponded to items conduct and social relationship.

METHOD.

We retrospectively reviewed consecutive patients seen between May 2014 and February 2016, treated with oral cannabis extracts with at least a 6-month follow-up period. Demographic/clinical data, type of seizures/epileptic syndrome, etiology, and number of previously used antiepileptic drugs (AEDs) were reviewed. Type of cannabis strain, extract, and dose (Figures 4, 5), CBD:THC ratio, frequency/severity of seizures before and after treatment, adverse events, and AEDs regimen during cannabis exposure were documented. Quality of life (QOL) changes were estimated using CAVE scale, and QOLIE-31-P, WHOQOL-BREF subscales.

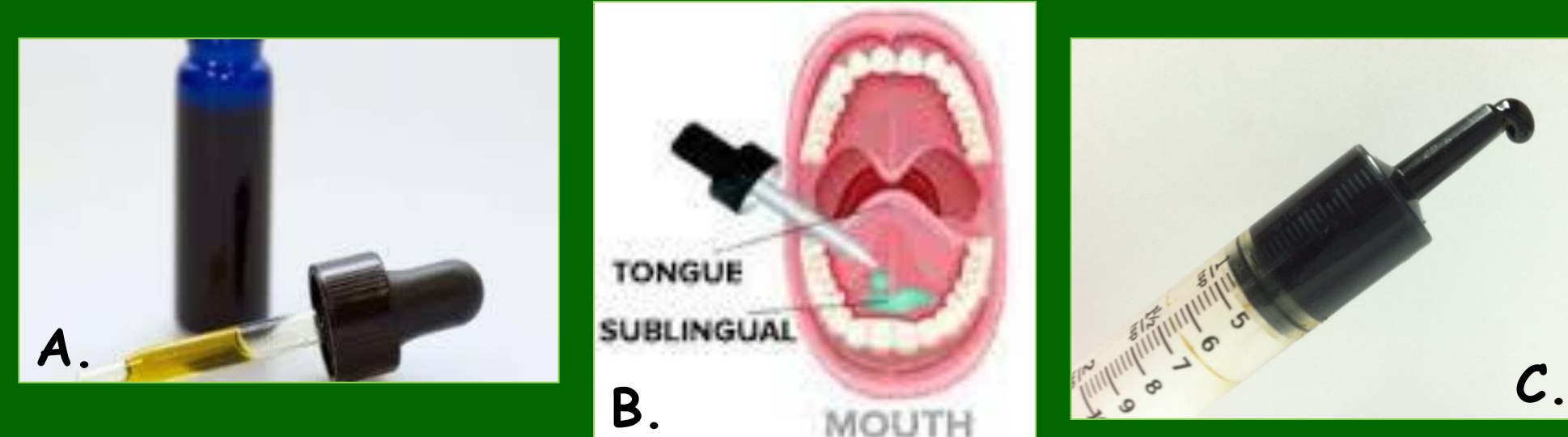


Figure 4. Types of cannabis extracts and delivery method: A. Macerated oil. B. Sublingual administration. C. Resin.

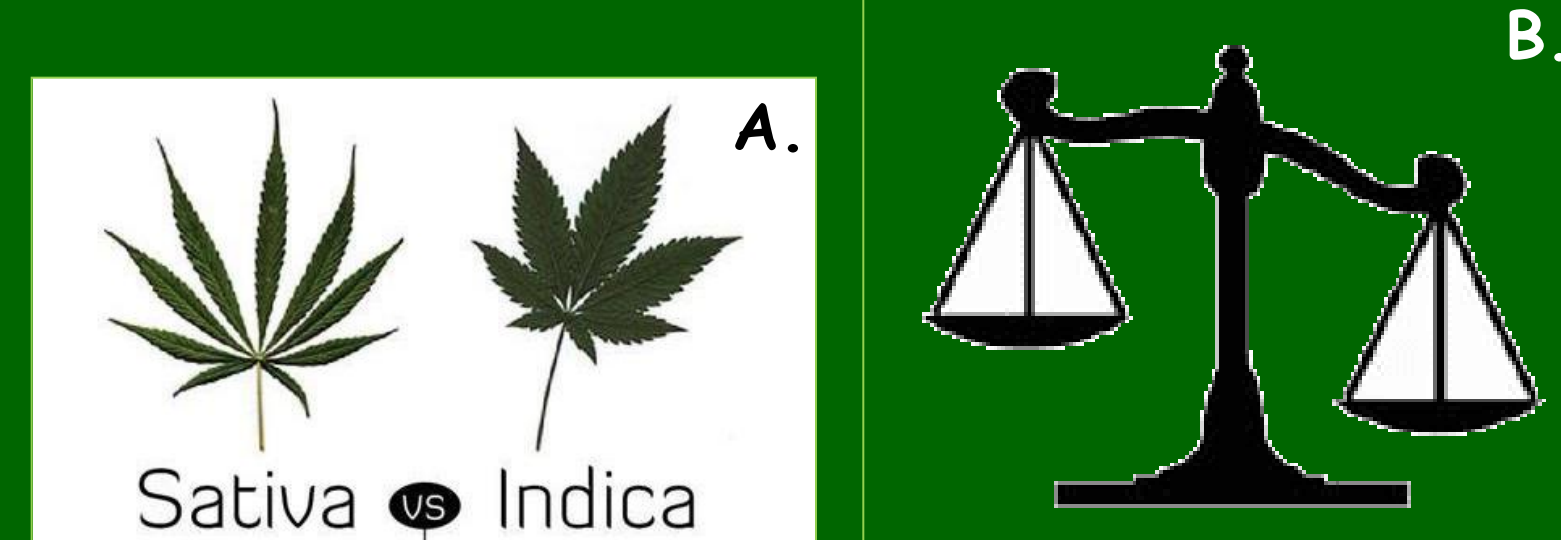
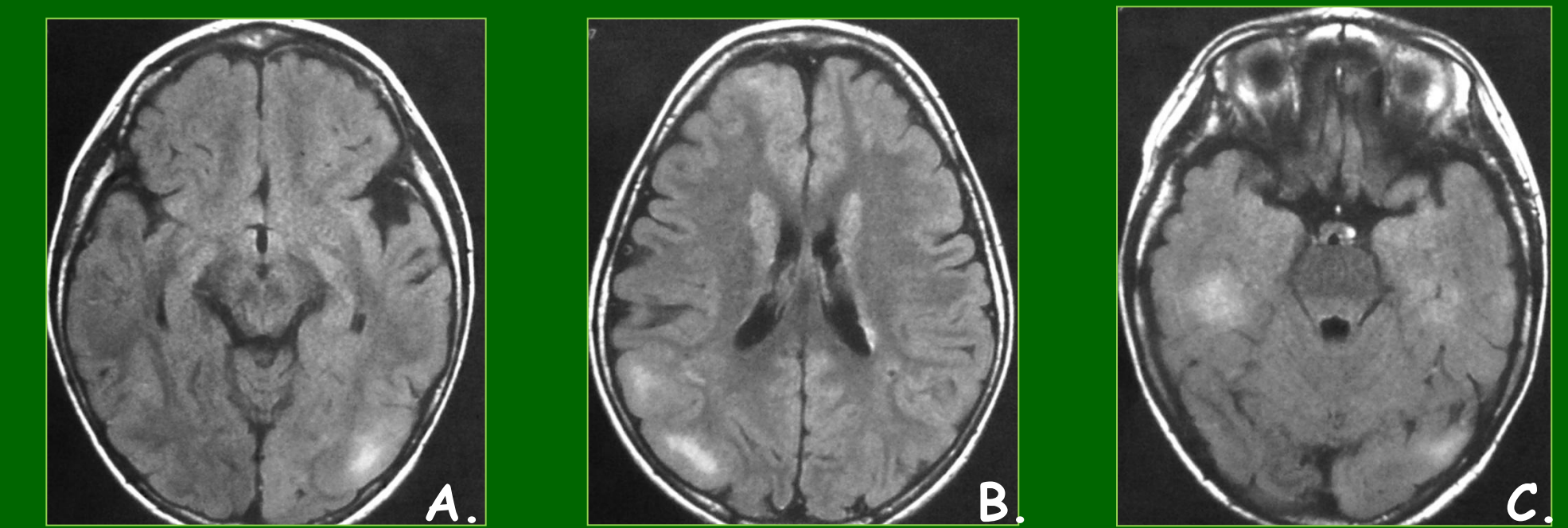
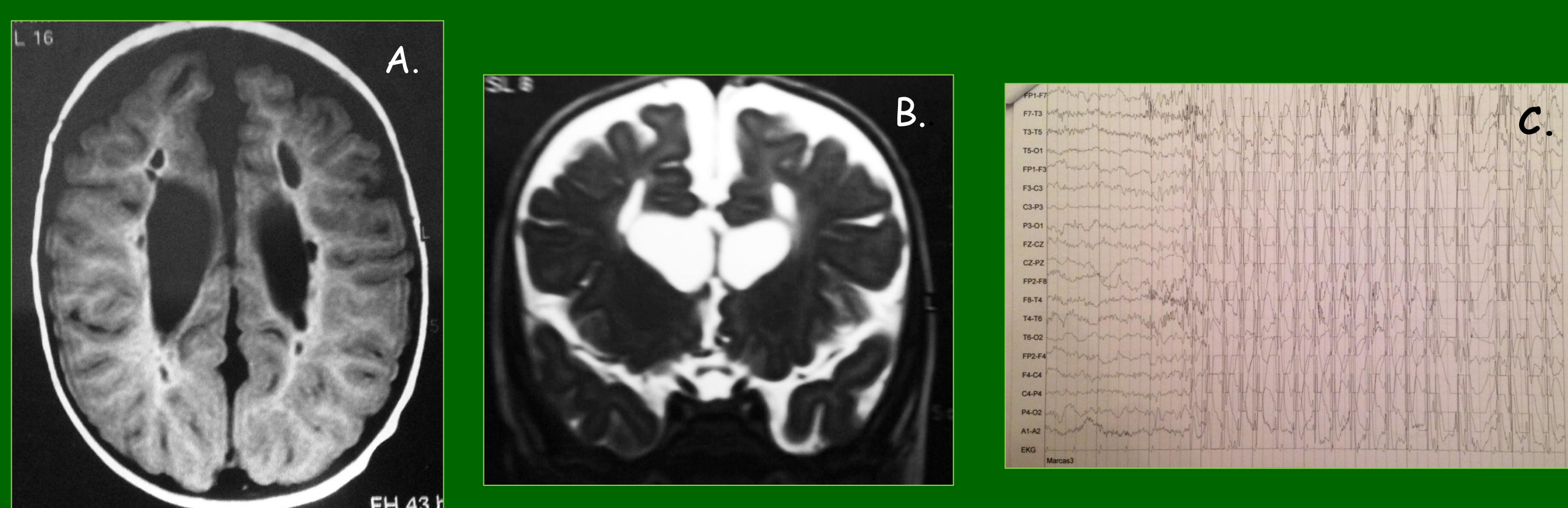


Figure 5. Relevance of cannabis strains (A) and their CBD:THC ratio (B) in the clinical response.



Case 2. 8 yo. girl with tuberosclerosis and refractory multifocal epilepsy. She was treated with 6 different AEDs without improvement and with severe adverse events, including aggressive behavior and self-harm. Axial images of her brain MRI are shown in upper figures (A,B,C). 90% of seizure reduction was observed with cannabis resin. Also, dramatical seizure severity reduction, and conductual/cognitive improvement were reported by her parents and teachers.



Case 1. 11 yo. boy with refractory epilepsy secondary to perinatal hypoxic-ischemic encephalopathy. Upper figures include two brain MRI images (A,B), and ictal EEG (C). High-CBD strains provoked seizure exacerbation and irritability. High-THC strains provoked dramatical seizure improvement, less spasticity, and also better sleep and conduct. The patient did not speak nor eat without assistance previous to cannabis use. After treatment he started to babble and to eat food by using his right hand.

CONCLUSION.

In this small series of patients with intractable epilepsy, oral cannabis extracts were much more effective than conventional AEDs previously used, with good tolerability. This has been also shown in other surveys and many case reports. Interestingly, some patients did not have good response or were aggravated by high-CBD strains, so the optimal therapeutic cannabinoid ratio could vary. Large randomized controlled trials are needed to establish efficacy and safety of cannabis extracts in epilepsy. Our Foundation is conducting in Chile the first double-blind, parallel group, and placebo controlled study of a standardized cannabis extract in children with pharmaco-resistant epilepsy.

Table 1. Epilepsy etiology.

Etiology	Number of patients
Brain malformation	3
Perinatal hypoxic-ischemic encephalopathy	2
Autism	2
Tuberosclerosis	2
Unknown	2

Table 2. Seizure outcome.

Seizure frequency reduction	Number of patients (%)
≥ 75%	5 (45,4%)
≥ 50-75%	2 (18,2%)
≥ 25-50%	1 (9,1%)
< 25% or aggravation	2 (18,2%)
seizure free	1 (9,1%)