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RESEARCH ARTICLE

Autism Spectrum Disorder Symptoms Improve with Combination Therapy Directed at Improving Gut Microbiota and Reducing Inflammation

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Abstract

Objective: To reverse autism spectrum disorders (ASDs) by normalizing the gut microbiome and reducing pro-inflammatory cytokine production.

Methods: Current evidence ties autism to high levels of brain inflammation and propionic acid produced by gut bacteria. In an effort to improve gut microflora and reduce inflammatory cytokines, patients consumed a combination of dietary supplements or antibiotics to correct small intestine bacterial overgrowth and consumed omega-3 (fish oil) and omega-9 (olive oil) to counter inflammatory dietary omega-6 fatty acids. Observations were made based on clinical follow-up and parent reports.

Results: Patient outcomes were dramatic and unprecedented. Within days of initiating this protocol, young children became more aware of their surroundings, making more eye contact and initiating social interactions. Many children began speaking within 2-8 weeks and improvement in all developmental areas was re-initiated. Within several months, teens and young adults also demonstrated recovery and resumed the development of social skills and language. Over 12-24 months, autistic behaviors faded, developmental deficiencies resolved, and a variety of features of autonomic function greatly improved. Within this time frame, most children under the age of seven became indistinguishable from their peers.

Conclusions: Recent research demonstrates a connection between ASDs and the gut microbiome, highlighting the need to more fully understand the "gut-brain axis" and how bacteria residing in the gut influence mood, learning, attention, awareness, development, and immune function. The observations described here are unparalleled in the treatment of autism and necessitate the attention of medical practitioners and clinical scientists.

Keywords: Autism (234), Developmental Disorders (228), Autonomic Diseases (1), Gastrointestinal (149), Neuropsychology/behavior (199)

Introduction

Autism spectrum disorders (ASDs) are highly associated with an abnormal gut microbiome and elevated inflammatory cytokines [1, 2]. Repeated exposures to antimicrobial agents (such as antibiotics, pesticides, and herbicides) have contributed to a global decline in gut microbial diversity. Dysbiosis is increasing among the population as depleted and imbalanced microbiota is sequentially transferred from mother to child [3]. Low biodiversity and other factors that slow intestinal motility increase the propensity of the overgrowth of colonic bacteria within the small intestine [4]. This overgrowth is implicated in the excessive production of propionic acid in autism [5].

In mice, certain species of gut bacteria influence social behavior [6], particularly those bacteria that produce propionic acid (PPA) as PPA crosses the blood-brain barrier and alters brain physiology [7]. A properly balanced microbiota also supports the integrity of the intestinal lining and a healthy gut-brain axis [8]. Furthermore, lipopolysaccharides shed by bacterial overgrowth penetrate the central nervous system (CNS) via bacterial translocation and systemic circulation resulting in primed-microglia [9]. The resulting impairment of pruning and neuronal repair mechanisms contributes to autonomic dysfunction from cumulative brain damage [10, 11] and the deficient synaptic/neuronal pruning observed in ASD [12].

A clinical protocol was developed based on the hypothesis that suppression of propionic acid production and the reduction of pro-inflammatory cytokines within the CNS would restore brain function by eliminating encephalopathic effect of propionic acid and normalizing microglia functions. This report describes the development and results of the protocol in children and young adults with ASD and provides a basis for further study.

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Methods

The following protocol was developed over the course of several years to reverse ANS dysfunction by targeting SIBO and reducing inflammation [13].

Rebalancing the gut microbiome

Inulin, a pre-biotic dietary fiber, is a fructo-oligosaccaride (FOS) derived from plant sources [14]. Inulin is not absorbed during digestion and enters the intestine where it ferments and lowers the pH of the intestinal lumen, changing the composition of the intestinal microflora [15]. A high-fiber diet has far-reaching effects, impacting mineral and vitamin absorption [16], hormones and mood, brain health, the gut lining, digestive function, and the immune system [17]. In young children, inulin was sufficient to produce results that suggested the resolution of bacterial overgrowth (resolution of diarrhea, food intolerance, and abdominal discomfort).

Daily oral administration of powdered inulin (NOW Foods, Bloomingdale, IL, USA) or Fiber Choice gummies (IM Health Science, Boca Raton, FL) was given starting at a dose of 1/8 teaspoon or equivalent. The dose was gradually increased until the patient achieved an improvement in eye contact and awareness of family members referred to as the "awakening"; that dose, typically between 1/4 and 1 teaspoon per day, was then maintained. In children over age ten and adults, inulin alone was often not sufficient to achieve an awakening; in this patient subset, the non-absorbable antibiotic rifaximin [18] was administered at 550 mg twice daily over a course of ten days.

Reducing inflammation and repairing the brain

The typical Western diet contains excessive amounts of linoleic acid, a pro-inflammatory omega-6 fatty acid while simultaneously being deficient in anti-inflammatory omega-3 fatty acids, particularly docosahexaenoic acid (DHA), which is necessary for brain development [19]. Fish oil contains both DHA and eicosapentaenoic (EPA). Extra virgin olive oil (EVOO) is 70-85% oleic acid, an omega-9 fatty acid capable of attenuating the inflammatory effects of excessive linoleic acid [20]. These two oils are essential components of the protocol; they not only provide essential nutrients for the brain, but also counter-balance the high levels of inflammatory omega-6 oils present in the typical Western diet [21]. The fish oil recommended to patients was produced by NOW Foods (Bloomingdale, IL, USA) or Nordic Naturals (Watsonville, CA, USA) (either liquid form, gel caps, or gummies) and California Olive Ranch EVOO (certified by the California Olive Oil Council). Fish oil and EVOO dosing was according to age (Table 1).

Special considerations

In some instances, the awakening period was characterized by extreme levels of anxiety, aggression, or emotional sensitivity and was disruptive to the family or dangerous for the patient and caregivers. In this case, inulin was temporarily discontinued and only the oils were administered for six to eight weeks to allow some improvement in emotion regulation before the reintroduction of inulin. The delayed introduction of inulin slowed the rate of neurological recovery but allowed for bacteria overgrowth and the sedative effect of PPA to return. When inulin was introduced later, a less emotionally intense awakening was observed, and the patient's rate of recovery seemed to accelerate.

(Table 1): Omega-3 from fish oil dosage according to age.

Age	Daily omega-3 (EPA and DHA) dosage
0-6 months	150 mg
7-12 months	350-450 mg
1-4 years	450-600 mg
5-7 years	600-1,000 mg
8-10 years	1,000-1,500 mg
11-14 years	1,500-2,000 mg
15-18 years	2,000-3,000 mg
Over 18 years	At least 3,000 mg of the DHA portion

Additionally, patients were counseled to avoid dietary sources of omega-6 containing oils as much as possible.

Results/Observations

Over the course of the first two to four weeks after introducing inulin or Rifaximin, parents noticed their children displaying greatly improved eye contact and acting more connected with the world around them. Children started seeking out parents for comfort or when they needed something and began making more purposeful gesturing. This initial period was referred to as the "awakening". Sleep patterns were variable during the awakening but typically improved within several weeks.

The "awakening" is likely due to the removal of the sedative effects of PPA produced by the bacterial overgrowth. This period occasionally presented with increased stimming, aggression, odd behaviors, loud noises, disrupted sleep patterns, increased emotionality, and constipation, among other less than desirable symptoms. These symptoms commonly resolved over the next few months with continued adherence to the protocol. Most exciting for parents was the return of speech or initiation of speech for the first time. Several case studies are described in the supplemental material.

Differences in recovery between regressive and neonatal autism and with comorbid conditions

The most dramatic recovery was witnessed in children with regressive autism occurring typically between one and three years of age. Many of these children manifested symptoms suggestive of developmental delay earlier in life, but if the features suggestive of autism occurred later, clinical improvement was highly likely. In contrast, children with significant features of autism from birth did not respond in a similar fashion.

Children with regressive autism and comorbid diagnoses such as Down syndrome, epilepsy, cerebral palsy, or traumatic brain injury seemed to attain a clinical "awakening" as well as re-initiate neurological development in a fashion similar to those without any comorbid diagnoses. Moreover, children with

autism attributed to genetic abnormalities that were previously assumed to be irreversible have shown improvements.

Interference from other supplements

Probiotics and digestive enzymes were found to interfere with the success of the protocol and were strictly avoided. Most patients were able to discontinue the use of nutritional and other supplements without consequence. Notably, the overuse of unnecessary vitamins, enzymes, antibiotics, and other supplements was found to interfere with the success of the protocol. We propose this likely reflects the delicate state of the brain of a young child recovering from inflammatory stress, such that even small doses of these ingredients were enough to aggravate the recovering physiology.

Discussion/implications for clinical practice

PPA produced via bacterial overgrowth in the small intestines impacts the brain and manifests as social avoidance behaviors, sensory issues, anxiety, stimming, and sleep disturbances [1]. Because infants inherit gut microflora from their mothers [3], bacterial overgrowth and diminished bacterial diversity is compounded with each generation. This implies that the incidence of ASD could increase substantially with each generation.

In addition to the cumulative depletion of microflora passed down from mother to offspring, pregnancy may worsen dysbiosis and increase inflammatory cytokines in the mother which may explain why children born shortly after an older sibling have a higher likelihood of developing ASD [22]. Exposure to maternal inflammation and depletion of omega-3 fatty acids *in utero* have also been associated with ASD [23], suggesting that mothers are likely experiencing the same neuronal distress from pro-inflammatory cytokine exposure [9].

Specifically, the diversity of bacterial species in the small intestine has been significantly diminished, allowing for colonic bacterial species including *Streptococcus, Escherichia, Staphylococcus, Klebsiella, Bacteroides, Lactobacillus,* and *Clostridium* to migrate into the small intestine [3]. Bacteria like Clostridia, which are typically populous in ASD patients [24, 25] and produce high levels of PPA, can have a profound, though reversible, effect on social behavior [1, 26].

Behavioral Improvement

The rapid onset of increased awareness, eye contact, and interaction observed after initiation of inulin or rifaximin was likely a sign that PPA-producing bacteria were reduced through the effects of inulin or rifaximin. Both inulin [15] and rifaximin [18] are capable of reducing the overgrowth of propionic acid-producing bacteria within the small intestine.

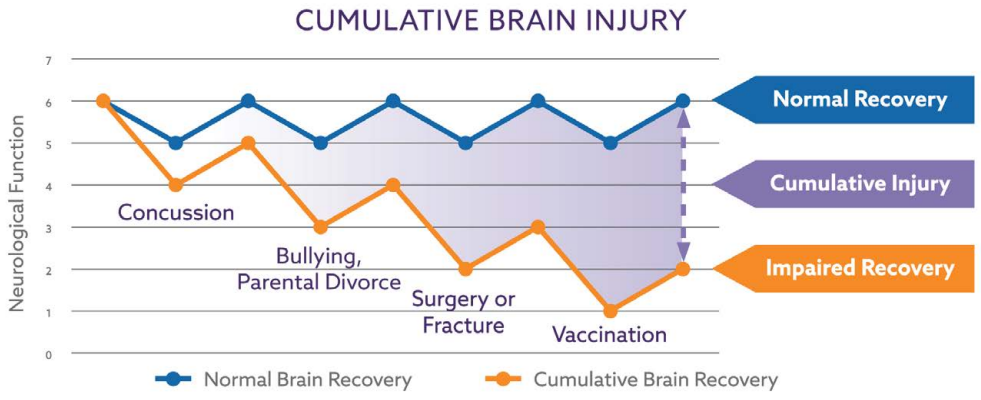
The families of bacteria capable of producing propionic acid are readily able to ferment carbohydrates. As such, diets commonly found effective in autism (GAPS, FODMAPS, Feingold, carbohydrate specific or gluten/casein-free) all restrict carbohydrates and are likely to result in a non-specific decrease in the overall bacterial load and production of propionic acid with a resulting improvement of symptoms.

Additionally, antimicrobials used to in autism to address pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), Lyme disease and co-infections, yeast/*Candida*, and parasites will also likely modulate bacterial overgrowth within the small intestine, potentially resulting in similar effects.

Future studies will be required to correlate cognitive improvements with serum PPA concentrations and the gut microbiome, but the dramatic improvement in awareness with inulin or rifaximin suggests alterations in the balance of intestinal bacteria is somehow related to the altered behavior in these children.

In addition to markedly improved awareness, many patients also displayed increased stimming, aggression, abnormal sleep patterns, and other disruptive behaviors. Rather than a worsening of behaviors, we believe these symptoms arise from underlying neurological dysfunction no longer suppressed by the sedating effects of propionic acid.

The neuroinflammatory process experienced by these patients also results in inefficient neuronal repair mechanisms and resulting cumulative brain injury (CBI) [27]. As a result, significant levels of brain injury accumulate (Figure 1) from frequent and seemingly insignificant physical, emotional, and inflammatory brain traumas that occur commonly in all humans [28].



(Figure 1): Cumulative Brain Injury (CBI) without proper repair mechanisms in place, brain injury accumulates from ongoing physical, emotional, and inflammatory brain traumas

More importantly, within a few months, these behaviors subsided, suggesting that the neurological repair mechanisms were re-activated with the assistance of the protocol. The re-initiation of the normal developmental progress in the children was also observed. LPS-primed microglias are increased in autism and are associated with decreased synaptic pruning, recruitment, and developmental delay [12].

We believe the supplementation with marine-derived DHA, an omega-3 fatty acid capable of triggering a phenotypic shift of pro-inflammatory primed-M1 microglia towards the M2-anti-inflammatory phenotype [29], is responsible for more normal microglial function and improved development in the children.

Interestingly, dietary fiber supplementation can decrease mercury in the brain [30], suggesting that a balanced gut microbiome may naturally help to prevent the accumulation of heavy metals [31] present in trace amounts within in water and food sources. It is therefore possible that, by maintaining a healthy gut population with this protocol, the body's natural ability to address the contribution of heavy metal toxicity theorized by others [32].

Additionally, while altered expression of many genes has been associated with ASD [33], it is possible that aberrant gene activation may return to normal after inflammation is controlled.

The older the subject, the slower the recovery

Younger patients appeared to experience faster recovery and a less intense "awakening" response, likely due to less time having elapsed since the disturbance of normal synaptic pruning and neuronal development. Another function of time is that fewer CBI from physical (concussive and sub-concussive), emotional, and inflammatory (vaccines, surgeries, fractures) traumas have had time to occur. All these brain injury types can cause cellular damage within the nervous system and would be expected to contribute the CBI burden.

In addition to the slower recovery rate, older subjects with autism can experience more intense levels of behavior during the "awakening" period.

Importance of the fatty acids

Omega-3 supplementation can assist in restoring neurological function following traumatic brain injury [34] and reduce seizures in mouse models [35]. Mice fed a diet high in EVOO perform better on tasks involving learning and memory [36, 37], implying an important role for these oils in the reduction of inflammation and enhancement of brain function.

Glutathione, the body's most powerful natural antioxidant, assists with the clearance of toxins and is depleted by PPA [38]. EVOO supplementation can stimulate glutathione production [39], suggesting that detoxification may be an additional downstream component of this protocol. EVOO supplementation can also reduce oxidative stress 39, which may play a role in reversing the mitochondrial dysfunction implicated in ASDs [1].

Pro-inflammatory cytokine production may result from multiple stimulants, including bacterial imbalance and bacterial translocation, excessive omega-6 fatty acids from vegetable oils and grain-fed livestock, deficient intakes of omega-3 fatty acids, vaccinations, surgery, fractures, and intake of advanced glycation end products from overheated, excessively cooked foods.

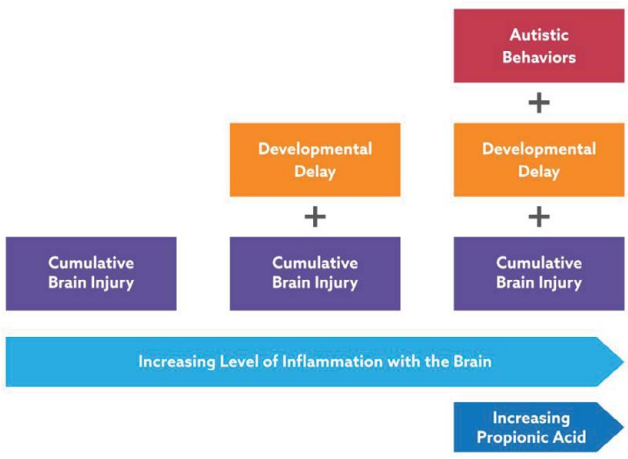
Diets high in omega-6 oils and low in omega-3 fatty acids, as found in most Western and industrialized countries, produce high levels of inflammation [21]. This effect can, however, be countered by supplementation with omega-3 fatty acids [40] and oleic acid found in olive oil [20].

Viewing autism and developmental disorders on the inflammatory-neurotoxic spectrum

Based on the degree of brain inflammation and the timing of symptom onset, autism and other developmental disorders can be categorized based on the severity of neuroinflammation, developmental disarray and toxic encephalopathy resulting from PPA (Figure 2).

Mild levels of neuroinflammation present with the late development of CBI (Figure 1) in teens manifesting as learning disorders, chronic depression, dysautonomia (headaches, anxiety, irritable bowel syndrome, premenstrual syndrome), and dysbiosis (hives, diarrhea, joint pain, anxiety, food intolerance, dysmenorrhea).

Moderate levels of neuroinflammation capable of disrupting microglia neuronal and synaptic pruning will present CBI manifesting at a younger age as well as delayed attainment of developmental milestones such as expressive and receptive language skills, sensory development, motor function, and socialization.



(Figure 2): Inflammatory Neurotoxic Spectrum Increasing levels of proinflammatory cytokines resulting from dysbiosis and omega-3: omega-6 imbalance leads to the impairment of neuronal/synaptic pruning/repair mechanisms and results in earlier and more significant levels of brain dysfunction. The additional systemic release of high levels of propionic acid is responsible for the additional clinical features associated with autism.

Moderate to severe levels of neuroinflammation in combination with the excessive production of PPA results in features commonly associated with autism (eye contact, facial expression, and gestures, sensory obsession or avoidance and repetitive behaviors) as well as severe degrees of developmental delay or even developmental arrest.

The dysbiosis seen in pediatric patients may present with colic, specific food aversions, diarrhea, recurrent hives, and/or constipation and abdominal cramping.

Conclusions

Based on the existing literature reviewed here and the observed success in treating ASD symptoms with this protocol, it is proposed that ASDs are the result of the culmination of five separate symptom-causing processes: (1) toxic encephalopathy from PPA and its derivatives; (2) impaired neuronal development *in utero* due to inflammation; (3) impaired neuronal pruning after birth due to inflammation; (4) impaired brain injury repair due to inflammation; and (5) possible genetic activation or damage *in utero* or after birth due to inflammation.

The observations described here imply an unprecedented opportunity to reverse the symptoms of autism and support brain development using high-quality, inexpensive, readily-available, food-based products. The protocol is easily implemented from home and can be done safely as a preventative in children as young as a few months old.

Controlled clinical trials involving physiological testing will validate the effects of all three components of the protocol. Small intestine bacteria are notoriously difficult to identify because stool testing is contaminated by colonic bacteria and largely inaccurate so improved methods of detecting autism-associated dysbiosis are needed. Brain imaging would also be useful to visualize the changes occurring in brain structure.

Additional studies are needed to determine the physiology that may differ among patients who do not respond to the protocol. It is possible that these individuals may have been exposed to such excessive levels of inflammation during fetal development that damage is more fundamental and difficult to reverse.

In the meantime, this protocol offers an opportunity to reverse the symptoms of autism and gives hope to families and individuals struggling with social engagement and developmental pathology. Patients and families are often able to de-escalate rehabilitative services, saving money, and return the family to a healthier emotional balance. By correcting bacterial overgrowth and reducing brain inflammation, a wide range of seemingly distinct childhood developmental issues can be addressed.

Case Studies

Pre-teen, regressive autism, male

Parents described an eight-year-old boy as having had severe reflux at the age of three months, a slight delay in speech at 12 months, followed by a regression at 18 months with complete loss of speech and eye contact with no obvious trigger. At eight years old, he only rarely spoke sporadic words out of context, had limited ability to use utensils, significant insomnia, self-isolated in his room with little interaction with siblings or family dog. He began the protocol in July 2017 at age eight with ¼ tsp powdered inulin, 1 tsp liquid fish oil, and ¼ tsp olive oil. Within eight weeks he displayed a noticeable increase in eye contact and speech; after four months, he was able to write in nearly complete sentences and speech became conversational. He no longer isolates himself in his room and eagerly plays with siblings and the family dog.

School age, regressive autism, female

A four-year-old girl presented with some delay in speech and motor milestones. As an infant, she underwent surgery for cleft palate repair at age nine months and regressed with loss of eye contact, worsening fine motor skills, and almost paralyzing social anxiety. She also developed recurrent hives on her face and torso as well as eosinophilic esophagitis requiring oral steroid and anti-histamine therapy. Prior to treatment she remained anxious, had limited speech, was constantly hungry, and struggled with insomnia. At age four she was started on daily fish oil (three Nordic Naturals Fishy gummies) and inulin (two Fiber Choice gummies); no olive oil was used at the time. Within three weeks, the subject's anxiety was greatly reduced, and she was able to transition into kindergarten without any episodes of severe anxiety. After five months on the protocol, speech and learning capabilities were greatly increased, hunger had declined, and the patient began to expand her food preferences. After eight months on the protocol, learning and speech were age-appropriate and she was able to discontinue medications for esophagitis.

Teen, regressive autism, male

A sixteen-year-old male presented with whispered, unintelligible speech, insomnia, high levels of anxiety, and aggressive and self-harming behaviors requiring several psychiatric medications. Chronic diarrhea and reflux were observed since birth. At age eighteen months, speech and eye contact decreased shortly after receiving vaccination. Onset of seizures was observed at age six and was controlled with medication. He began the protocol at age sixteen with six NOW DHA-500 capsules, olive oil added to food and Rifaximin at 550 mg for ten days. Within three months, his anxiety and sleep issues were greatly improved, diarrhea was resolved, and speech was more clear and coherent. After seven months, speech continued to improve with occasional five- to six-word sentences and aggression was decreasing significantly allowing for the tapering and discontinuation of the psychiatric medications.

Adult, regressive autism, down syndrome, male

Adult male with Down syndrome hit developmental milestones until the age of six when he fell while climbing a shelving unit and sustained a concussion. He then regressed into autism with loss of most speech and became withdrawn and anxious. At

the time of presentation, he spent a great deal of time trying to compress his shirt collar against his chest with his chin. His mother described this as one of many odd behaviors. He also suffered from eczema, chronic diarrhea, and chest pains from reflux. As a teen he began to develop aggression and angry outbursts. At age 34 his anxiety and aggressive behaviors seemed to worsen, and speech was limited to wants and needs. He began the protocol at age 36 with Rifaximin at 550 mg for ten days, six DHA-500 capsules, and 2 Tbsp olive oil. After two months, reflux and chest pain ceased, eczema improved, speech increased, and aggressive behaviors stopped. After six months, the odd behaviors described by his mother had resolved, anxiety was greatly reduced, and speech had increased with improved conversation, more words being strung together, and improved clarity of thought process.

Adult, regressive autism, Lennox-Gastaut Syndrome, female

Development appeared normal for this adult female between birth and ten months. At ten months old she developed seizures shortly after vaccination and was placed on anti-epileptic medications. From age ten months to five years, she had limited capacity to speak, read, and write. At five years old, the patient was again vaccinated, and she experienced a marked increase in the frequency of seizures. Many anti-epileptic medications were utilized with limited effectiveness. At age 12 years, the patient experienced a worsening of her symptoms after undergoing surgery. She became more withdrawn, her speech was almost non-existent, and she would no longer attempt to read or write. As an adult, she was experiencing one to three seizures per day and several throughout the night (a combination of drop attacks and grand mal despite being on four anti-epileptic medications). She did not make eye contact, did not want to be touched, and spent most of her day rocking in a seated position with her legs drawn toward her chest. She did not speak except for occasionally muttering the name of someone that was unknown to the family (likely the result of hallucination) and showed very little interest in the use of writing or drawing implements. She began the protocol at the age of twenty-two with Rifaximin at 550 mg for ten days, 2 Tbsp olive oil, and six NOW DHA-500 capsules. Within two months she regained eye contact, spoke single words with intent and direct eye contact with her parents, began sleeping more at night, her anxiety was reduced, and daytime seizure frequency declined from one to three per day to two to three per week. This improvement occurred with the protocol despite her mother stopping one of her anti-epileptic drugs. She also stopped sitting with her legs drawn up and rocking, and instead began sitting upright with minimal fidgeting during a 30-minute office visit. After eight months on the protocol, her speech continued to improve, becoming more clear and appropriate to situation, and included both Spanish and English words as the family speaks both. She was also able to write and spell her name despite having had no direct instruction on writing the alphabet. Seizures reduced to two to three daytime seizures per month despite additional discontinuation of anti-epileptic drugs. After eighteen months on the protocol, she was able to attend a daytime program but had outbursts of anger and aggression after sitting for prolonged periods. She was observed trying to steal things from the grocery store and having child-like tantrums when told she could not take them with her. At this point, daytime seizures were completely gone despite tapering off her final anti-epileptic drug.

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