CASE REPORT

My Experience Learning About Autism

我对自闭症的认识经历

Mi experiencia de aprendizaje sobre el autismo

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I remember the first time I heard the word "autistic." I was 10 years old, and my mom mentioned that someone had a child who was autistic. I was confused because I mistook her description as "artistic."

In April 2001, our first child, Isaiah, was born. My wife, Lanier, was concerned that he had autism at about 11 months of age, but I did not recognize his obvious problems, even though he was not responding to his name, was obsessed with spinning objects, and did not play with toys appropriately. He also had no language, did not walk until 18 months, and had significant gastrointestinal (GI) problems including severe reflux requiring medication and chronic diarrhea. At 19 months of age, Isaiah was diagnosed with autistic disorder.

During the process of his evaluation for possible autism, which involved day-long testing with a developmental pediatrician, psychologists, and therapists, I thought that they would say he had autistic tendencies but that nothing was actually wrong. When Isaiah was then diagnosed as having severe autism, I was quite surprised. We were told that Isaiah would probably need to be placed in an institution eventually and that there were no proven treatments for autism, except for applied behavioral analysis (ABA) therapy, which we started immediately. There was one glimmer of hope on that fateful day, however. While we were being told that Isaiah would probably never speak and that he might not even learn how to make animal noises, he picked up a pig toy and said "Oink, oink."

When Isaiah was diagnosed with autism, Lanier was pregnant with our second son, Joshua, and he was born in early 2003. We watched him very closely, and when he was 5 months old, we took him in for a 2-hour visit with a developmental pediatrician who declared that his development was completely normal. Unfortunately, 3 weeks later Joshua started developing autistic behaviors. At first we thought he was mimicking Isaiah, but it soon became apparent that Joshua had developed autism—despite the fact that we tried to do things to "avoid autism," including breastfeeding and not vaccinating Joshua up until that time. Joshua also developed many of the problems that Isaiah had, including chronic GI problems.

Lanier and I then began the process of searching for potential treatments for autism. Lanier started talking to other parents of children with autism, and they told her about nutritional supplements and restricted diets that helped their children. I was in a university setting at the time in the family medicine department, and I approached the pediatricians who treated children with autism to ask them about supplements, diets, and other treatments for autism. I remember being told that there were no studies in the literature reporting that a gluten-free, casein-free (GFCF) diet was effective and that no studies existed that supported nutritional supplements for treating autism. That was in 2004.

I was trained during residency in evidence-based medicine, so I was accustomed to critically examining the evidence for the treatments I used in clinical practice. I can remember doing extensive literature reviews during residency on topics such as treating high cholesterol to prevent heart disease and treatments for hypertension. However, because I was told there were no effective treatments for autism, I did not consider any treatments except ABA therapy, even though Lanier wanted to pursue other treatments that she heard about from other parents. I decided that these treatments (supplements and diets) were "quack" treatments. For some reason, I did not examine the medical literature to see which treatments were proven to help autism at that time. I decided that the only thing I could do was to work hard so that we could afford the "quack" treatments that Lanier wanted to pursue. These treatments did not seem harmful, so I did not see a problem with trying them.

Around that time, we took Isaiah to a gastroenterologist to determine why he had chronic diarrhea. I remember thinking it unusual when the doctor stated that the diarrhea was secondary to autism and that no testing was needed. I distinctly remember asking him if we should do a stool test to look for things such as infections, etc, and being told that it was not necessary. I accepted what the doctor told us because he was a specialist. It was not until several years later that I realized that GI abnormalities, including dysbiosis and inflammation, are very common findings in children with autism, and this evidence was already available and published in the medical literature (by 2003) at the time Isaiah had seen the gastroenterologist.[1-12]

Around 2004, Lanier decided that we should attend a conference that was being held by the Autism Research Institute (ARI). I was reluctant to go at first,

but then I decided to hear what "quack treatments" were being promoted. I remember being quite shocked that there seemed to be studies of treatments that were available for autism that appeared to be beneficial. I heard several speakers talk about the GFCF diet being helpful and about certain nutritional supplements that could be beneficial. Immediately after that conference, I went to the library at the university to do a search on PubMed concerning some of these treatments. It was then that I discovered published studies for the adverse effects of certain foods in children with autism spectrum disorders (ASD)[1,8,10,13,14] and multiple studies reporting that the GFCF diet was beneficial, at least in a subgroup of children with ASD.[15-24] Though it certainly can be argued that these were not the most rigorous studies, the point is that I had been told such studies did not even exist, and it was at that point that I realized I needed to review the medical literature for myself. I also found evidence in the medical literature for other treatments in children with autism, all published by 2003, such as vitamin C,[25] vitamin B_6 and magnesium,[26,27] melatonin,[28-30] vitamin A,[31] dietary tryptophan,[32] digestive enzymes,[33] L-carnosine,[34] galantamine,[35] fish oil,[36] and other nutritional supplements.[22]

Around that time, I remember seeing a child with autism in clinic who had severe self-injurious behaviors and not knowing how to help him. He had sores all over his body from hitting and biting himself, and he lived in a group home. He also had chronic GI problems. I did not realize at that time that certain foods[13] and GI problems[37] could cause severe behavioral problems in some children with autism and that treatment for these could alleviate some of the "autistic behaviors" that resulted from these problems. At that time, I was not aware of the 25 studies published in the literature up until that time (including eight double-blind, placebo-controlled studies) reporting improvements in autistic behaviors, including self-injurious behaviors and aggression, with the use of oral naltrexone.[38] (Interestingly, to date, there are more studies reporting that naltrexone is beneficial for autism than any other medication, yet it is not a US Food and Drug Administration (FDA)–approved treatment for autism, probably because it is generic and there is no pharmaceutical company to champion it.) Unfortunately, because I did not have the knowledge about naltrexone and other available treatments, I was unable to substantially help this child. I also wondered if Isaiah and Joshua would develop the type of problems that he had.

As I was starting to become aware of the published literature in autism treatments (from attending the ARI conference and doing literature searches), I was also seeing improvements in my children as a result of the "quack" treatments that Lanier was giving to Isaiah and Joshua. For example, a GFCF diet helped both children with their chronic GI problems, and supplements such as fish oil lowered hyperactivity. My wife became interested in hyperbaric oxygen treatment (HBOT), which other parents were reporting was helping their children with autism. Very reluctantly, I agreed to purchase a HBOT chamber for them to get treatments. I remember one day after Isaiah had done about 20 hours of treatments in the chamber. At that time, he was only saying one word at a time. We had a gate that prevented him from going up the stairs, and it was locked. I was lying on the couch, and he came up to me and said, "Open the gate, please." I almost fell off the couch! This was the first time he put words together for me. The only change we made during that time was HBOT as we wanted to specifically track this treatment to see if it would help. After this undeniable improvement in Isaiah using HBOT, I searched PubMed because I was sure someone had studied this treatment in autism, but to my surprise, there were no published studies. Because of this, I decided that this treatment needed to be studied, and that led to three studies, including a double-blind, controlled study. These studies found that HBOT improved biochemical markers and certain autistic behaviors in some children with autism.[39-41]

I then started on a journey of systematic reviews of the medical literature concerning autism treatments. For example, because some physicians were stating that no nutritional supplements had been shown to help children with autism, I decided to perform a systematic review and meta-analysis (with Richard Frye, MD, PhD, Arkansas Children's Hospital, Little Rock) on the best-studied supplement in autism, which was melatonin. The review identified 18 studies reporting improvements in children with autism using melatonin, including five double-blind, placebo-controlled studies.[42] I also became interested in studying novel and emerging treatments for autism and published a systematic review where I ranked the evidence for nutritional supplements, dietary changes, and medications.[43]

Around that time, I also began to realize that autism was diagnosed solely by the observation of behaviors[44] and that the diagnosis did not necessarily explain why the child had autism. I began to understand that many of the autism treatments I was learning about targeted the underlying pathophysiology of autism and in that sense, were not treating autism per se but treating these underlying physiological problems potentially contributing to autism. For example, some children with autism who have GI reflux can become aggressive and hit themselves and other people.[37] If this is not understood, then their presentation can be misinterpreted as "autistic behavior" instead of behavior arising from severe GI pain. As another example, in some children with autism, aggressive and self-stimulatory behaviors can be related to epileptiform activity.[45]

I began to see that if metabolism was disturbed in some way, this could contribute to "autistic behavior." Over time, I became interested in metabolic and other

problems that could be contributing to autism symptomatology that were also potentially treatable. One condition that fascinated me was cerebral folate deficiency (CFD), as it can cause a reversible form of autism that is treatable. CFD is a neurometabolic syndrome characterized by low levels of 5-methyltetrahydrofolate (5-MTHF) in the brain despite normal systemic folate levels. One common cause of CFD is an autoantibody that binds to the folate receptor-α (FRα), making it nonfunctional and blocking the transportation of 5-MTHF from the blood into the central nervous system. Interestingly, cow's milk contains soluble FRα antigen, which is 91% similar to human FRα. Autoantibodies to the FRα cross-react with the soluble FRα antigen in cow's milk, increasing the concentration of autoantibodies and resulting in worsening of CFD, while elimination of cow's milk lowers the autoantibody concentration and improves CFD symptoms. This may explain why parents report improvement with a milk-free diet in some children with autism.[46,47] Notably, some cases of CFD are due to mitochondrial disease.[48,49] To date, three studies have reported an association between CFD and Rett syndrome,[50-52] seven studies have reported that CFD is associated with autism in some children,[53-59] and five studies have reported the presence of FRα autoantibodies in children with autism, some of whom also had CFD.[54,56,57,60,61] In a recent study, we reported on 93 children with ASD who had concentrations of FRα autoantibodies measured in the blood, and 75.3% were positive for at least one autoantibody.[61] Taken together, these studies of children with concomitant autism and CFD reported that treatment with oral folinic acid (leucovorin, 0.5 to 2 mg/kg/d) resulted in various improvements ranging from partial improvements in communication, social interaction, attention, and stereotypical behavior to complete recovery of both neurological and ASD symptoms.[62]

My research interest is now focused on metabolic and other problems that may contribute to autism symptoms and that are also treatable.[63] These conditions include mitochondrial dysfunction,[64-67] inflammation,[68] oxidative stress,[68] environmental toxicant exposures,[68] and seizures.[69] A great deal of information has been learned about autism since my children were diagnosed. Every day, more and more studies concerning autism are appearing in the literature. Several recent studies have reported "recovery" or the loss of autism in some children.[56,70-73] These factors as well as reports of recovery in some children give me a great deal of hope for the future concerning autism.

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