Diet Therapy for Alternating Hemiplegia of Childhood

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Abstract

Alternating Hemiplegia of Childhood (AHC) is among the rarest, genetically mediated diseases. It varies from child to child, and also from time to time in its effects. There are therapeutic pathways that may yield improvement sufficient to manage the pathology, allowing for nearly normal development. This basic essay outlines a known dietary therapy that may ameliorate many cruel AHC symptoms, without waiting for distant research to bear unknown fruit.

Rare diseases have often been called orphan diseases for good reason. There is little profit incentive for major drug companies, and there are multiple other diseases with more victims awaiting continuous "annuity" medications.

Nevertheless, any one child suffering from rare Alternating Hemiplegia of Childhood (AHC) or similar dystonia suffers just as much as any other child challenged by a more common severe disease. Furthermore, progress against one disease syndrome, however rare, may help accelerate clinical progress on similar and associated diseases.

Elements of the Proposed Therapeutic Model

Alternating Hemiplegia of Childhood challenges between one person in a million, and one in a hundred thousand. The victim numbers are both rare and elusive, thus accounting for the 10x discrepancy. There is no way to predict before conception who will be afflicted, and the syndrome typically does not clearly emerge until several months after birth. Victims may improve over several years, at least partially, or even regress. There are degrees and aspects of affliction, and therapists can only hope for development and enhanced functioning over time.

My proposed strategy is not to first design a brute CRISPR attack on the offending gene or genes, even though gene-editing technology could have great merit eventually. My approach is to now help eliminate specific toxic elements, such as allergens synergized by defective genes, most commonly *mutated ATP1A3*. It is not enough to correct specific genes, if other offending proteins are still present and capable of causing autoimmunity.

Consider the famous/infamous *Rubik's Cube*: Hold one in your hand, and you are holding both the puzzle and all the elements for discovering its confined solution. Holding all solution elements will not alone give you the solution. Elements must be seen both individually and in association. AHC research is now in a holding-the-Cube phase. My therapeutic model should generate a major functional amelioration of this evil syndrome. The AHC puzzle's solution is already in hand, so to speak. We need to orchestrate its elegant functional solution without needless delay.

Think too of the *fire triangle*, where all three elements of heat, oxygen, and fuel are needed for fires. Just remove any one, and there can be no fire.

[Any recommendation in this thesis is not to be construed as a medical diagnosis and/or prescription. Any therapy, dietary or otherwise, will be decided between individual families and their physicians. This essay only sets forth some serious ideas that should first be expeditiously explored by AHC researchers.]

The very common disaster of Alzheimer's is increasingly being understood as in part a brain toxin problem, not just a random accumulation of amyloid plaques. Recent studies in 2019 have found that deep sleep helps the brain clear itself from brain toxins related to potential Alzheimer's. From this perspective any genetic "nature" element is to some degree synergized by the "nurture" element of diet. Alzheimer studies are many and varied. Nevertheless, the element of life choices is commonly considered for senior therapies. The less frequent phenomenon of early onset Alzheimer's presents somewhat differently, with less of a life-choices component, and more elements related to family genetic histories.

AHC seems to be initiated and driven mostly by idiopathic *de novo* genetic defects in specific genes. Young children don't have multiple years to slowly accumulate brain debris similar to that in elderly dementia patients, nor is their pathology the same. Nevertheless, the therapeutic goal of reduced or eliminated symptoms is similar.

Toxins could be incrementally removed by daily outflowing CSF and lymphatic vessels, for processing by liver cells. Any "garbage removal" flow most likely will be secondary to the primary dietary therapy recommended herein, where allergens are not part of the diet. Think of the ounce of prevention being worth a pound of garbage-removal cure. One of the key presentations of AHC is how dystonic symptoms will often decrease overnight. There thus may be something to the idea of cerebrospinal fluid (CSF) draining poisons away overnight, while sleep fasting, some of the trigger molecules consumed by day.

It appears that physical and/or psychological stress in several forms may trigger enhanced production of brain toxins in AHC patients. Correlation among other disease syndromes has been well documented involving various allergies. People of all ages experience similar stress triggers from common allergies, but only a rare few also develop AHC. A likely difference is that people with, say, celiac disease do not also have the very rare

idiopathic mutations that synergize AHC, even when common gluten triggers are the same.

There are many potential experimental paths to follow within this model. Some have been looked at, but there is much more opportunity for symptomatic progress. For example, not all cases of AHC are of equal severity, and many young children emerge into adult lives that are somewhat symptom free, even while still consuming some gluten. Others have a more severe prognosis, with wheelchairs, inability to speak, and so forth.

I do not believe the different disease progression paths are random. I suspect the differences can be causally identified, leading to better therapeutics for all AHC victims. My proposed model could therefore provide a helpful bridge between allergic inconvenience and health crises.

AHC belongs to the greater category of dystonia diseases that also affect adults. With this functional commonality in mind, I suggest that the mechanical model of removing autoimmune toxins from the CSF could work for any age group: from young childhood, to young adulthood, to elderly ages. Let us not be too optimistic, as we are not anywhere talking panacea.

Even if my removal model is very successful for one disease syndrome, it may be less successful with other apparently similar challenges. Also, just because AHC can be more challenging during childhood – key mutated genes remain in the cerebellar brain throughout life, even among those with various levels of improvements.

A better version of my model involves keeping sensitive brain cells, such as cerebellar Purkinje cells – including their axons and dendrites with several thousand connections – free from specific attacking allergens in the first place. Gliadin proteins are found within wheat, barley, and rye. Gluten is the dietary vessel, and several gliadins are the toxins that stimulate the autoimmunity. It is not necessary to isolate any of the offending gliadin proteins,

as they are all packaged together within gluten. Remove dietary gluten, and all gliadin offenders are gone.

Celiac disease management mostly involves the strategy of keeping all gliadins away from sensitive nerve cells in the upper small intestine. To treat episodic AHC we must consider that other nerve cells beyond those in the small intestine are also allergenic targets. Interestingly, whereas celiac disease does not require mutated ATP1A3 sodium pump genes, the majority of AHC cases are associated with such rare genetic mutations.

This basic observation was reinforced by an important 2013 neurological study at the Howard Hughes Medical Institute on Mendelian inheritance and episodic disorders, typically found with sodium pump dysfunction: "These observations have cemented the channelopathy paradigm, in which episodic disorders are conceptualized as disorders of ion channels." Again, AHC is an episodic disease. Purkinje cells are responsible for the cerebellar ion channels, and they are the nerve cells damaged by the gluten dietary component, yielding acute T-cell mediated synaptopathy.

Nerve Cells and AHC

People get excited about the level of "brain power" associated with modern supercomputers, as well as the tantalizing potential of futuristic, organic-DNA and quantum computers, also powered by electricity. However, the very powerful thinking unit that has designed this digital intelligence is itself a tiny organic "computer," our cortex brains. Even self-programming AI systems have long been launched by humans.

I once took an English class taught by a Rhodes scholar. One of the tools he used to help us appreciate how little we know about the core elements of language was this simple exercise: He asked us to precisely write down how to tie a dress shirt's tie. If you think this exercise is trivial, try writing it precisely with ordinary words, and no accompanying hand visuals. One lesson here is how simple Reality is "unreal" in its beautiful complexity.

The mammal brain that is our glory, and possibly our collective unforeseen suicide weapon, has evolved over hundreds of millions of years. Our rate of higher cognitive evolution has, during the last ten thousand years, accelerated its now hominid complexity, reaching virtual hyper-evolution within the last two industrial centuries. Our resident Stone Age brain structures have been "left behind" by our emergent cerebral synapses, and interfacing Internet electronic libraries. Most significant is how ambitious humans have learned to pick and choose among all the "random" online data, finding greedy associations that have enabled us to create the uniquely dangerous Anthropocene epoch.

It is fairly easy to design primitive brain studies in the lab. In the real world things are quantitatively much more complex, and qualitatively very dialectical and nuanced. When we examine adult human brains we weigh them at about three pounds. When we look at them from an engineering perspective we encounter something like 100 billion cells per brain. There are about 1,000 connections among an individual cell's axons and dendrites. That all yields about *100 trillion synapses* sparking inside our small brain cavities. How can the quaint concept of standard IQ test numbers measure such vast mental potential?

Not all brain cells are equal. The population of one type of brain cell in the cerebellum, the Purkinje cells, has up to about 7,000 synaptic connections each. The number of up to 200,000 connections per cell is declared in one source.

I mention the Purkinje cells, because they are not just in each brain. They are critical to heart regulation. Other types of nerve cells are involved with intestinal interiors and celiac disease. We know them as the body's "second brain." Mostly, Purkinje cells populate a layer of our cerebellar tissue. It is precisely among the cerebellar Purkinje cells that allergenic antagonists do their dirty work – resulting in Alternating Hemiplegia of Childhood (AHC), synergized by mutations in the ATP1A3 and other genes.

There has been solid research supporting this gluten ataxia thesis among Purkinje cells, starting most prominently in 2001 by

M. Hadjivassiliou, MD, and several others. This lead author is a noted neurologist in England who investigated this vexing allergy problem with several other doctoral researchers.

Another study from 2002 involving the same lead researcher and his team comes to a similar conclusion, which is that:

> "Patients with gluten ataxia have antibodies against Purkinje cells. Antigliadin antibodies cross-react with epitopes on Purkinje cells."

Dystonia Diseases

AHC resides on the more severe half of the dystonia spectrum. The *New Oxford American Dictionary* defines dystonia as: "a state of abnormal muscle tone resulting in muscular spasm and abnormal posture, typically due to neurological disease or a side effect of drug therapy."

The same gene that causes evil in AHC patients is also involved in rapid-onset dystonia–parkinsonism. An individual's specific genetic mutation may not have caused AHC, but later in life other forms of dystonia can be associated with severe symptoms. Here could be a less-than-obvious opportunity in another autoimmune syndrome that may be ameliorated through dietary manipulation.

Celiac Disease

There has been a lot of research on celiac disease, yielding one key therapy that relates to AHC. Because so many people have celiac disease, in adults as well as children, pharmaceutical firms have been looking for the magic patentable cure. However, their best "cure" to date is the dietary elimination of offending food proteins, a process that cannot be patented. Even though there is no profitable magic bullet on the horizon for AHC, it is possible to look at autoimmune celiac disease as providing one therapeutic model that can help guide us toward managing the worst of AHC, short of that elusive "cure."

The Lancet has a collection of references relating to gluten-sensitive enteropathy. New evidence, gathered by six doctoral researchers, pointing to extra–intestinal presentations without enteropathy are found there. This finding supports the idea that aspects of AHC may also be present beyond cerebellar Purkinje cells, and include other potentially important aspects of gliadin-mediated autoimmunity.

It is possible that the embryonic developmental association between gut nerve cells and cerebellar brain cells may also be relevant beyond the vagus nerve – leading to an unnoticed neurological link between autoimmunities in celiac disease and AHC. We don't need to first understand all genetic associations to design an effective ounce-of-prevention diet therapy.

AHC Management Strategies

Considering the modestly funded AHC "search for the cure," things will only continue to go from bad to worse for thousands of young AHC sufferers. Glacial progress is unsatisfactory. AHC is a global human species challenge, except in areas where rice and corn are the grains of choice. The two problems today are money for research AND the all-or-nothing goal of cure seekers.

Sometimes less is more, as has been well documented for celiac disease therapy. The same ameliorative strategy should apply for AHC, because nerve cells in different parts of the body are involved in both syndromes. Different regions of the body determine how gliadin autoimmune allergy expresses itself in different ways. Removal of offending allergens from the daily diet benefits all parts of a human body, and are independent of mutated gene accelerants. Additionally, dietary manipulation is possible from childhood to old age, and is available everywhere.

The mere diagnosis of AHC usually involves expensive genetic tests far beyond the resources of family doctors, and poor local communities. By the time a child reaches the age where his or her syndrome is obvious, that child may have lost critical months

or years of opportunities for intervention. Purkinje cells once damaged cannot be fully repaired. The AHC syndrome from an early age typically delays and perverts development in ways beyond simple locomotion, including speech and intelligence. In brief, the earlier the better for management.

Additional ataxia data was presented by nine researchers. Here is an important observation they made:

> "A heterogeneous spectrum of clinical manifestations caused by mutations in *ATP1A3* have been previously described. Here we report two cases of infantile–onset cerebellar ataxia, due to two different *ATP1A3* variants. Both patients showed slowly progressive cerebellar ataxia without paroxysmal or episodic symptoms."

What Needs To Happen Now

We are now at the end of 2021. The revealing published data referenced herein go back to 2001. Quality research data from esteemed neurological scientists have all pointed to a primary problem that is likely to be ameliorated by a simple program of gluten-free dietary modification for AHC. They have pointed to elements needed to quickly solve this "AHC Rubik's Cube," but none have proposed or begun the needed field-study solution.

Consider the "AHC fire triangle": Remove either the gluten allergy, or the ATP1A3 mutation, and there is no AHC. The third "leg" of this triangle is the precious human being's life.

An elegant, one-variable, field study with a representative sample of young AHC patients can yield significant developmental progress without the need to do anything more. The benefits to patients and their families would be profound. This study would be both humane and scientific. Additional genetic disorders could also benefit from lessons learned. There is no reason for delay. Who will be the lead scientists for this key dietary study in 2022?

AHC Addendum

May 6, 2022

The main essay above was written just over four months ago. In the interim everybody has been focused on Covid in all facets. Covid variants are still with us, and so too is AHC. Furthermore, in the interim there has been slightly more interest in AHC with the publication of my original essay. However, there has been no field study initiated for testing my amelioration hypothesis.

One of the main reasons for my waiting a third of a year to add this addendum has been how little improvement is typically made by those early with severe AHC, even with the removal of gliadins within the diet. I well know of one case where his path has been typical, even after a gluten-free diet was started some months after birth. This case will remain anonymous.

The persistence of autoimmune cerebellar ataxia from Purkinje cell damage minimizes the improvements that can be made, even without additional gluten. Nevertheless, a gluten-free diet has in this one case demonstrated that the downward health spiral can be partially ameliorated, and the precious child can live a much better life. Indeed, even a partial AHC therapeutic victory should be counted as a major life victory.

I have spent hours pondering what else could be done short of expensive genetic testing during pregnancy, which is not possible on a mass scale for such a rare condition. Recently, I considered what can be done as a broader prevention, which should help eliminate both AHC and other gluten-related autoimmune diseases. My goal is to achieve something that doesn't cost or disrupt, and still provides an optimal outcome.

Cerebellar gluten ataxia is an autoimmune condition. It is not common, and less so than gluten-related celiac disease. It is still much more common than AHC, which additionally involves mutant ATP1A3 genes, and possibly other similar mutations.

We can rank the frequency of disease appearances, from most common to least common as follows. Any of these four could have or develop into serious consequences:

non-celiac gluten sensitivity
>
celiac gluten sensitivity
>
gluten ataxia
>
AHC

Gluten's gliadin proteins are antagonistic to every Purkinje cell's activity and structure, even within a person who "only" has the most common autoimmunity. That person could develop new ataxias in later life following a gluten-filled diet, without obvious symptoms in youth. Purkinje cells are also within our hearts.

The extremely rare AHC syndrome also involves something not found in typical celiac disease: mutated ATP1A3 genes. It is the evil synergy between gluten autoimmunity *plus* the effects of the specific gene mutations that launch evil ATP.

Looking at the descending-frequency syndrome list above, there is one commonality: from developing life within the womb and thereafter there is gluten sensitivity. This is the key. Even though a loving mother may herself have none of these Purkinje sensitivities with gene mutations, she may carry a developing embryo and fetus that does.

Ideally, she only needs to start a strict gluten-free diet right after she knows she is pregnant. It would be optimal to maintain that diet for her nursing baby, as some gliadins are transferred by mother's milk to her baby and his developing brain.

There are many different gluten-free diet choices that make it easy for most pregnant mothers to adopt. Some cultural cuisines have many gluten-free choices. In the modern world we can

easily pivot for optimum health of our newest family members. The question remains: Who should pivot, and who should not?

With the above in mind, it would be wise to do one of two types of AHC field trials. Obviously, we won't get much quality data from strict gluten-free diets during pregnancy, given that AHC is so rare and virtually random.

On the other hand, if there is a family history of celiac disease the autoimmunity risk is enhanced, since at-risk Purkinje cells are also found in the digestive tract. It could be possible to achieve statistically significant data for family celiac risk, even while AHC is too rare and elusive.

I would therefore recommend conducting initial field trials with the original gluten-free postpartum study model advanced before this addendum. I have seen some amelioration in the one case that I personally know. Any functional AHC improvement, or lessening of even worse future effects, is highly desirable – and positive results can quickly be demonstrated with a small study sample size.

To date there have been no such trials as I have suggested. There have however been other proposed models that simply don't work (such as the ketogenic error). Time is of the essence for this important AHC gluten sensitivity study.

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