

ORIGINAL RESEARCH

SYNDROME OF ALLERGY, APRAXIA, AND MALABSORPTION: CHARACTERIZATION OF A NEURODEVELOPMENTAL PHENOTYPE THAT RESPONDS TO OMEGA 3 AND VITAMIN E SUPPLEMENTATION

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Objective • Verbal apraxia is a neurologically based motor planning speech disorder of unknown etiology common in autism spectrum disorders. Vitamin E deficiency causes symptoms that overlap those of verbal apraxia. Polyunsaturated fatty acids in the cell membrane are vulnerable to lipid peroxidation and early destruction if vitamin E is not readily available, potentially leading to neurological sequelae. Inflammation of the gastrointestinal (GI) tract and malabsorption of nutrients such as vitamin E and carnitine may contribute to neurological abnormalities. The goal of this investigation was to characterize symptoms and metabolic anomalies of a subset of children with verbal apraxia who may respond to nutritional interventions.

Design and Patients • A total of 187 children with verbal apraxia received vitamin E + polyunsaturated fatty acid supplementation. A celiac panel, fat-soluble vitamin test, and carnitine level were obtained in patients having blood analyzed.

Results • A common clinical phenotype of male predominance, autism, sensory issues, low muscle tone, coordination difficulties, food allergy, and GI symptoms emerged. In all, 181 families (97%)

reported dramatic improvements in a number of areas including speech, imitation, coordination, eye contact, behavior, sensory issues, and development of pain sensation. Plasma vitamin E levels varied in children tested; however, pretreatment levels did not reflect clinical response. Low carnitine (20/26), high antigliadin antibodies (15/21), gluten-sensitivity HLA alleles (10/10), and zinc (2/2) and vitamin D deficiencies (4/7) were common abnormalities. Fat malabsorption was identified in 8 of 11 boys screened.

Conclusion • We characterize a novel apraxia phenotype that responds to polyunsaturated fatty acids and vitamin E. The association of carnitine deficiency, gluten sensitivity/food allergy, and fat malabsorption with the apraxia phenotype suggests that a comprehensive metabolic workup is warranted. Appropriate screening may identify a subgroup of children with a previously unrecognized syndrome of allergy, apraxia, and malabsorption who are responsive to nutritional interventions in addition to traditional speech and occupational therapy. Controlled trials in apraxia and autism spectrum disorders are warranted. (*Altern Ther Health Med*. 2009;15(4):34-43.)

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Disclosures

Claudia R. Morris, MD, is the inventor or co-inventor of several Children's Hospital & Research Center Oakland patent applications, including one for a nutritional formula licensed to Nourish Life, PharmaOmega; has served on scientific advisory committees for Merck and Icagen; received an educational stipend from INO Therapeutics; and has been a consultant for Biomarin, Gilead Sciences, Inc, and the Clinical Advisors Independent Consulting Group.

Accumulating evidence suggests that developmental disorders such as apraxia/dyspraxia (developmental coordination disorder), attention deficit hyperactivity disorder (ADHD), dyslexia, and autism spectrum disorders (ASD) are conditions involving a deficiency of long-chain polyunsaturated fatty acids (PUFAs).¹⁻¹⁶ Studies demonstrating the importance of sufficient docosahexaenoic acid (DHA) for brain development¹⁷ have led to the routine addition of DHA to most commercially available infant formulas. Supplementation with omega 3 fish oil is a safe intervention^{4,18} that has led to improvements in behavior, motor skills, and language in many children affected by the aforementioned disabilities,^{2,4-6,9,10} and recent placebo-controlled trials demonstrated benefits for children with autism¹⁹ and ADHD.²⁰ Anecdotal evidence collected over the years by the CHERAB foundation (Communication Help, Education, Research, Apraxia Base, a

Web-based support group and resource center for families with children suffering from childhood apraxia of speech with more than 7700 members) lists thousands of children who experienced significant improvements in speech production and coordination after supplementing with PUFA formulas that include both eicosapentaenoic acid (EPA) and DHA.²¹ Additionally, PUFA levels (DHA and EPA) are low in autism,¹¹ as well as in children with verbal apraxia (VA) prior to supplementation (Marilyn Agin, MD, unpublished data). In an open-label study of 19 apraxic or apraxic and autistic children, Agin et al demonstrated that even low-dose PUFA supplementation contributed to a marked shift in speech and language production and affected behavioral/social parameters, including eye contact and attention, beyond what could be expected with speech therapy alone.²²⁻²⁴ An additional case study similarly demonstrates that PUFA supplementation in children with apraxia in conjunction with speech therapy increased pre-speech behaviors (eye contact, attention to task), speech and language production (single sounds, word, and sentence production), imitation skill accuracy, and decreased inconsistent imitation errors, distractibility, and groping behaviors.²⁵

VA is a neurologically based motor planning disorder of unknown etiology,²⁶ although there is evidence of genetic influences related to apraxia,²⁷ familial speech,^{28,29} and neurologically based disorders such as dyslexia and ADHD.^{4,30,31} Confusion around this condition is reflected by the vast number of terms used to define it, including childhood apraxia of speech, developmental apraxia, developmental dyspraxia, speech apraxia, and speech dyspraxia, to name a few. For the purposes of this article we will refer to it as VA. Approximately half of children with ASD have some degree of apraxia,³² although not all apraxic children are autistic. Children with this disorder find it very difficult to correctly pronounce sounds, syllables, and words despite intense effort (Table 1). Intelligibility is poor, and some children remain completely speechless and require the use of augmentative communication devices or a picture-exchange communication system.²¹ Many children with VA present with homogeneous symptoms of neurological dysfunction that affect coordination, muscle tone, and sensory issues^{21,26,33} in addition to expressive speech delay, suggesting a common underlying mechanism of disease. Vitamin E deficiency causes a constellation of symptoms³⁴⁻³⁷ that overlap those of speech apraxia, limb dyspraxia, hypotonia, and sensory integration dysfunction (including abnormalities in proprioception, vestibular sensation, and pain interpretation) that often occur in VA and ASD. Low bioavailability of vitamin E will create an environment within the cell membrane where PUFAs are vulnerable to lipid peroxidation and early destruction. This can lead to a functional PUFA deficiency and neurological sequelae (Table 2) that may be reversible through supplementation of vitamin E and PUFA. In addition, PUFA supplementation

SAFETY OF VITAMIN E SUPPLEMENTATION

Vitamin E supplementation is safe across a broad range of doses.^{1,3} The Linus Pauling Institute site has detailed information on safety: <http://lpi.oregonstate.edu/infocenter/vitamins/vitaminE/>. Jacqueline Stordy, PhD, a nutritionist and author of *The LCP Solution: The Remarkable Nutritional Treatment for ADHD, Dyslexia & Dyspraxia*, states doses up to 3000 IU/day of vitamin E are safe for a 3-year-old child. The developing nervous system appears to be especially vulnerable to vitamin E deficiency because children with severe vitamin E deficiency from birth who are not treated with vitamin E develop neurological symptoms rapidly. In contrast, individuals who develop malabsorption of vitamin E in adulthood may not develop neurological symptoms for 10 to 20 years. The RDA and upper tolerable limits (UL) are listed on the Linus Pauling site; however, it should be noted that these numbers are generated for the normal population. Treatment for neurological symptoms of vitamin E deficiency is 100 to 200 mg/kg/day, which surpasses the UL for normal individuals. Neurological complications are reversible if treated early. Recent studies describe flaws in earlier vitamin E investigations,⁴ as doses of 1600 to 3200 IU/day are needed to reverse oxidative stress.⁵ Even at 3200 IU/day, vitamin E clearly still works as an antioxidant rather than the theorized potential to become a pro-oxidant.⁵ The Food and Nutritional Board specifically notes that "clinical trials of doses of alpha tocopherol above the UL should not be discouraged" so that important new information on safety and efficacy can be obtained.⁶ Given concerns about vitamin K antagonism, coagulation studies should be followed if high doses are used, and families should be counseled to watch out for increased bruising. Additional supplementation with vitamin K also should be considered with long-term therapy with high-dose vitamin E. It is difficult to determine the ideal dosing regimen for verbal apraxia without further investigation; however, the neurological symptoms of apraxia overlap those of a true vitamin E deficiency and respond to doses in the range used for the treatment of neurological complications of vitamin E deficiency. Further study is required in this area, but our preliminary data suggest that neurological improvements that occur with vitamin E in verbal apraxia are dose-dependent. Children experiencing the most significant recovery were those using doses >2000 IU/day under the watchful care of their pediatricians. Doses ≤1500 IU/day are believed to be unlikely to cause bleeding complications in rat studies done to determine the UL. No recommendations can be made without controlled clinical trials in children with VA determining long-term safety and efficacy. Doses below the published UL of 1500 IU/day should be used until more information is available, although higher doses ultimately may be needed.

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TABLE 1 Red Flags for Verbal Apraxia**Signs and Symptoms of Verbal Apraxia****Early symptoms** (first year of life)

- Limited babbling, “quiet” baby
- Feeding problems, difficulty transitioning to solids
- Poor imitation skills
- History of reflux
- Drooling that exceeds typical expectations
- Lack of oral exploration
- Signs of oral apraxia (unable to imitate tongue protrusion or a kiss)

Later signs

- Elaborate gestural communication (unless there is an associated severe “dyspraxia”)
- Limited consonant and vowel repertoire
- Receptive > expressive language; normal cognition
- Vowel distortions
- Inconsistent errors, ↑ errors with ↑ length of utterance
- Excessive equal stress on each syllable
- Difficulty repeating the same syllable sequence without errors

Common neurological “soft signs”

- Hypotonia (truncal)
- Poor gross and fine motor coordination
- Motor planning difficulties
- Sensory integration/self-regulatory issues
 - Abnormal pain sensation, proprioception, and vestibular sensation
 - Delayed or mixed dominance

increases utilization of vitamin E in the body.³⁸⁻⁴¹ These two supplements may have a synergistic effect at higher doses. We summarize data gathered on 187 children with VA to more clearly characterize this neurodevelopmental syndrome.

METHODS

Since CHERAB was founded more than 8 years ago to provide information on apraxia, emotional support, and a medium for information exchange, thousands of children with apraxia have demonstrated improvement in speech and coordination after initiation of PUFA supplementation. Soon after a recovery story was shared online, numerous families began to describe advancements that vastly surpassed those of PUFA alone using vitamin E combined with PUFA. We set out to characterize the symptoms and metabolic anomalies of a cohort of children with VA that may respond to nutritional interventions. A questionnaire was posted on the CHERAB site requesting information from families with a child diagnosed with VA who had tried PUFA+ vitamin E therapy to share their experiences with supplementation, both good and bad. A positive response to therapy was defined as improvement in speech, babbling, coordination, imitation, eye contact, behavior, sensory issues, and/or the development of pain sensation. Details of any perceived adverse effects were also solicited. Age and gender were recorded. Information specifically on the presence or absence of an ASD diagnosed by a medical professional and any other comorbid medical diagnoses was requested. Families were also asked (yes/no) whether coordination

difficulties (dyspraxia), sensory issues, abnormal pain sensation, low muscle tone, gastrointestinal (GI) problems, or food allergy were present in their children. GI symptoms were defined as recurrent abdominal pain, recurrent vomiting, colic, or gastroesophageal reflux disorder (GERD) warranting medications or multiple formula changes, chronic diarrhea, and/or constipation requiring use of laxatives.

Families reported their experiences with PUFA and vitamin E supplementation online or through personal communication. A celiac panel, fat-soluble vitamin test, and carnitine level were obtained in patients having blood analyzed. Results of these tests were often in the form of “high,” “low,” or “normal” without actual values reported. Doses of vitamin E used range from 400 IU to 3000 IU a day, with the majority of families using 800 IU a day divided into 2 doses and some with an additional gamma-tocopherol supplement (200-800 mg/day). Doses and brands of PUFAs also varied; however, the majority of families used supplements that contained 280 mg DHA and 695 mg EPA per dose in liquid or capsule form, given with a meal 1 to 3 times daily.

This data collection project received expedited approval by the Institutional Review Board at Children’s Hospital & Research Center Oakland, California.

RESULTS

Data were analyzed on 187 children with VA (age range 2-15 years; median age 4 years). A common clinical phenotype of male predominance (148/187, 79%), sensory issues (≥49%), low muscle tone (≥32%), ASD (≥27%), coordination difficulties (≥24%), food allergy (≥14%), and GI symptoms (≥13%) emerged. Not all families reported the presence or absence of these symptoms, so the prevalence of comorbidity in our VA cohort is likely underestimated.

A total of 181 families (97%) reported dramatic improvements in a number of areas including speech, imitation, coordination, eye contact, behavior, sensory issues, development of pain sensation, and GERD symptoms. No serious adverse events were reported; however, 22 families described a similar pattern of transient atypical behavior that included increased moodiness, temper tantrums, hyperactivity, and crying that generally lasted between 1 to 3 weeks before subsiding. This was usually accompanied by notable improvements in speech, babbling, imitation, and/or coordination. One family reported nosebleeds. Five families reported no improvement, and 1 family reported worsening aggressive and irritable behavior that was unacceptable, and the supplements were stopped within a week. Five of the 6 nonresponders carried a dual diagnosis of VA and ASD.

COMORBID CONDITIONS REPORTED WITH VA

The following conditions were diagnosed by a medical professional in addition to VA: ASD (n=50/77, 65%), ADHD (n=8), seizure disorder (n=4), central auditory processing disorder (n=3), global developmental delay (n=3), Phelan-McDermid syndrome (n=3), and a single case each of infantile spasms, deafness, Williams syndrome, Smith Magenis syndrome, chromosomal microdeletions, dwarfism, Prader Willi syndrome, fetal alcohol syndrome, complex I mitochondrial disorder, Sanfilippo syndrome, and brain tumor. Not all families reported the presence or absence of these conditions, so the true

TABLE 2 Clinical Features of Vitamin E Deficiency

Sign	Abetalipo-proteinemia	Chronic Cholestatic Hepatobiliary Disease	Other Fat Malabsorption Disorders	Genetic Vitamin E Deficiency
Hyporeflexia, areflexia	++	++	++	±
Cerebellar ataxia	++	++	++	++
Loss of position sense	++	++	+	±
Loss of vibratory sense	++	++	++	++
Loss of touch, pain	+	±	+	—
Ophthalmoplegia	+	+	+	—
Ptosis	+	+	±	—
Muscle weakness	+	+	+	+
Pigmented retinopathy	++	±	+	—
Dysarthria	+	±	+	±

++ indicates always present; +, commonly present; ±, inconsistently present; —, absent.

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denominator is unknown. Information on the presence or absence of a diagnosis of ASD was specifically requested and 77/187 families provided a “yes” or “no” response.

Comorbid Neurological “Soft Signs”

Parents reported the following symptoms in order of frequency. Not all families reported the presence or lack of these symptoms, so the true denominator is unknown. There is likely a bias in the responding group toward those experiencing this comorbidity. Results are documented as the number of families responding “yes” to presence of sign/total number of patients who responded and percentage of positive answers: sensory integration dysfunction (92/95; 97%), with 32/90 (36%) describing high pain tolerance and abnormal pain sensation; low muscle tone, typically in the trunk (n=61/69; 88%); and coordination difficulties/dyspraxia (45/48; 94%).

Gastrointestinal Symptoms and Allergy

For the presence of GI symptoms, 25/30 (83%) responded “yes.” One child had a gastrostomy tube for severe GERD. Food allergy and/or asthma was reported in 28/32 (88%) children. Both GI symptoms and allergies were reported in 19 of the 33 (58%) symptomatic children. The food allergies were often multiple and most frequently to gluten, milk, or peanut when specified.

Laboratory Analyses

A variety of blood testing was performed and reported in 26 children. A summary of abnormal laboratory results is provided below.

Plasma alpha-d-tocopherol levels: A broad range of levels was reported in 13 children, both low (n=3), high (n=4), and normal (n=6) prior to supplementation. Presupplementation plasma levels do not appear to reflect clinical response to vitamin E.

Plasma carnitine levels: Low plasma carnitine (total and free) was reported in 20/26 (77%) children. Total carnitine levels were often 50% to 70% below the lower limit of normal, suggesting a moderate to severe deficiency.

Antigliadin immunoglobulin G antibodies: An abnormal celi-

ac panel with high antigliadin IgG antibodies was identified in 15/22 (68%) children tested. Ten children had subsequent human leukocyte antigen (HLA) testing done, and 100% revealed the presence of a “gluten-sensitivity” HLA genotype.

Fat-soluble vitamins: Reports of vitamin D deficiency were found in 4/7 patients screened, and early signs of rickets were identified in 2 children. One child had signs of rickets recognized on wrist films.

Plasma selenium and zinc: One of 2 boys tested had a significant selenium deficiency, and 2/2 screened positive for zinc deficiency.

HLA testing: Genetic testing was performed on 10 boys, 100% of whom carried a gluten-sensitivity HLA “DQ” allele (6 with DQ1 gene, known to be associated with neurological complications of gluten sensitivity, and 4 with DQ2 associated with classic celiac disease). Antigliadin IgG antibodies were elevated in 7 boys genetically tested. Two of the boys with a negative celiac panel were on a gluten-free diet from 6 to 36 months at the time of testing for clinical symptoms of gluten sensitivity. Intestinal biopsies done on 4 boys were negative for “classic” celiac disease, although 1 demonstrated villous atrophy, and a second demonstrated gross but nonspecific inflammation of the small bowel not consistent with Crohn’s disease.

Cholesterol: Low plasma cholesterol level was identified in 3/4 patients tested.

Qualitative fecal fat Sudan stain: A fat malabsorption syndrome was identified in 8/11 boys by qualitative fecal fat studies. At least 4 boys had further confirmation of fat malabsorption by 72-hour quantitative fecal fat collection.

DISCUSSION

We describe a new syndrome of allergy, apraxia, and malabsorption (Table 3; Box), which is likely one class of a larger apraxia phenotype. The apraxia phenotype often coexists with ASD and vice versa, suggesting overlap in these conditions that requires further characterization. We also have identified a disease paradigm of neurological dysfunction emulating symptoms of low vitamin E bioavailability in VA independent of genotype that responds to a safe nutritional intervention. The relationship

TABLE 3 Clinical and Metabolic Features of Syndrome of Allergy, Apraxia, and Malabsorption (SAAM)

Sign	SAAM
Verbal apraxia/severely delayed expressive speech*	++
Allergy (particularly food intolerances like gluten sensitivity)	++
Fat malabsorption	++
Oral apraxia	+
Hyporeflexia, loss of postural reflexes*	+
Cerebellar ataxia/coordination difficulties/limb dyspraxia*	+
Loss of position sense*	±
Loss of vibratory sense*	±
Loss of touch, pain*	+
Muscle weakness/low tone, especially truncal*	+
Carnitine deficiency	+
Autism spectrum disorder	+
Variable nutritional deficiencies	+
Low plasma cholesterol	+
Gastrointestinal symptoms	±
Frequent infections—recurrent otitis/sinusitis (? immune dysregulation)	±
Cognitive delay	—

*Symptoms overlapping those of vitamin E deficiency associates with neurologic disease.
++ indicates always present; +, commonly present; ±, inconsistently present; —, absent.

of carnitine deficiency, gluten sensitivity/food allergy, and fat malabsorption with VA is a novel observation, suggesting that these children deserve a more comprehensive metabolic workup than what is current standard practice. This report represents the largest summary of information on children with VA to date. Recommended laboratory analyses based on the data presented here are listed in Table 4.

Malabsorption and increased consumption of antioxidants during oxidative stress⁴²⁻⁴⁶ may account for increased utilization of vitamin E and other fat-soluble vitamin deficiencies.^{12,47,48} Children with ASD have evidence of global inflammation^{49,50} and increased oxidative stress.⁵¹⁻⁵⁵ Though mechanisms contributing to the motor planning issues of VA are unknown, the potent antioxidant properties of vitamin E may contribute to the beneficial effects described in this cohort.^{42,43,56,57} A recent article demonstrating that a water-soluble vitamin E derivative is capable of attenuating a number of neurobehavioral alterations observed in mice exposed postnatally to methylmercury supports the neuroprotective benefits of vitamin E from oxidative stress in an animal model.⁵⁸ Inflammation of the GI tract,^{53-55,59-62} food allergies, and gluten sensitivity^{47,54,63-67} commonly found in apraxic and autistic children may further contribute to depletion of antioxidants and malabsorption of critical nutrients such as vitamin E^{65,68-73} and carnitine,⁷⁴⁻⁸¹ with subsequent fatty acid metabolism dysfunction and a cycle of increased oxidative stress. Although benefits of a gluten-free diet in patients with ASD have been described,^{47,63,67} conflicting reports are found in the literature.⁶⁴ Elevated plasma antigliadin antibodies commonly found in ASD⁸²⁻⁸⁶

TABLE 4 Suggested Apraxia Workup*

Bloodwork

- Plasma vitamin A, D, E, K levels, zinc, copper, PIVKA-II (protein-induced in vitamin K absence-II; more sensitive test for vitamin K deficiency); methylmalonic acid (screen for B₁₂ bioavailability).
- Carnitine (total and free) and acyl-carnitine level
- Celiac panel (to include antigliadin IgG, IgA, tTG, and total IgA level)
- HLA testing for DQ1, DQ2, and DQ8 alleles (if further clarification needed)
- Serum iron, ferritin, TIBC
- Comprehensive metabolic panel (including LFTs, albumen)
- Complete blood count with differential
- Food allergy testing (RAST, skin-prick)
 - CK level, lactic acid, pyruvate, plasma amino acids, and urine organic acids if not already done as part of metabolic workup; consider cholesterol/lipid panel
 - Chromosome analysis for karyotype, fragile X, and microchip array (if suspect genetic syndrome)

Stool

- Malabsorption screen: stool for qualitative fecal fat, pH, and reducing substances (72-hour quantitative fecal fat collection is indicated if qualitative fecal fat test is abnormal).

*IgG indicates immunoglobulin G; IgA, immunoglobulin A; tTG, tissue transglutaminase; HLA, human leukocyte antigen; TIBC, total iron binding capacity; LFT, liver function test; RAST, radioallergosorbent test; CK, creatine kinase.

may contribute to neurological symptoms, as these antibodies crossreact to Purkinje fiber cells in the cerebellum,⁸⁶ brain cells known to be damaged in ASD.^{51,87} Alternatively, elevated antigliadin antibodies may represent the signature of increased gut permeability and inflammation independent of celiac disease. Screening for antigliadin antibodies may help to identify a subgroup of children who would benefit from dietary gluten elimination. Nearly 70% of children screened in our cohort had elevated antigliadin antibodies, remarkably higher than the 12% reported in the general population,⁸⁸ although the meaning of this observation remains to be determined. Genetic susceptibility for gluten sensitivity can be screened for by HLA testing, as there is a strong association with the “DQ” alleles. The gluten sensitivity HLA gene DQ1 is associated with gluten ataxia and neurological complications of gluten sensitivity.^{65,88-91} Positive intestinal biopsies for “classic” celiac disease are identified in only a third of patients with neurological complications of gluten sensitivity carrying the DQ1 HLA gene,⁹¹ suggesting a neurological variant of celiac disease or perhaps a novel disease state associated with gluten sensitivity that warrants further investigation in VA and ASD. Although our sample size is small, the 100% frequency of this HLA genotype is high in our cohort, given its prevalence of about 15% to 30% in Caucasians.^{92,93}

The etiology of low cholesterol is unknown but could be the consequence of a fat malabsorption syndrome. Alternatively, it could reflect variations in cholesterol metabolism, already described in some children with autism,^{94,95} that warrants further exploration in syndrome of allergy, apraxia, and malabsorption. The recent observation that Niemann-Pick C1-Like 1, a key transporter

involved in intestinal cholesterol absorption, also co-transport alpha-tocopherol⁹⁶ is intriguing. Aberrations in such a transport system could plausibly result in an apraxia phenotype. Interestingly, clinical manifestations of Niemann-Pick C⁹⁷ share similar characteristics with the apraxia phenotype and may provide further clues to a common paradigm.

Nearly 80% of the children with VA screened had evidence of a carnitine deficiency, a novel observation in apraxia that has been reported in ASD⁷⁷ and is also a common feature of celiac disease.^{74-76,81} Low carnitine may be a cause rather than an effect of gut inflammation, as recent studies support an obligatory role for carnitine in the maintenance of normal intestinal function.⁹⁸ However, low carnitine can be a clue to a number of metabolic disorders⁹⁹ and is associated with hypotonia.¹⁰⁰ More importantly, an untreated carnitine deficiency may adversely impact cardiac function and is associated with sudden death¹⁰¹⁻¹⁰⁷ and dilated cardiomyopathy.¹⁰⁸⁻¹¹⁰ Carnitine supplementation will prevent such complications and is warranted once a carnitine deficiency is identified. Carnitine also plays a critical role in fatty acid transport into the mitochondria and may contribute to abnormal fatty acid metabolism.⁹⁹ Children with a neurological diagnosis of VA should be screened for carnitine deficiency given its high prevalence in our cohort and the preventable complications associated with it. Those children with carnitine deficiency warrant referral to a metabolic specialist for further evaluation and treatment.

Plasma levels of vitamin E are not helpful in identifying responders in this cohort, likely because levels in plasma do not always reflect levels in organs such as brain and muscle. Abnormalities in alpha-tocopherol transport into the brain and nervous system are additional mechanisms that could account for the neurological complications despite apparently adequate plasma alpha-tocopherol levels. Genetic abnormalities of the alpha-tocopherol transport protein have been described and are associated with neurological complications.¹¹¹ Alpha-tocopherol transport protein has been identified in brain as well as liver.^{112,113}

Like autism, cases of VA are also on the rise.¹¹⁴ Many of these children have significant coordination difficulties that warrant early screening, as they may not become clinically evident until the child reaches kindergarten age, when motor deficits begin to affect self-care and academic tasks.¹¹⁵ Early intervention with occupational therapy may improve outcome. Accumulating data clearly demonstrate that speech and coordination disorders go hand in hand.^{116,117} Similar to VA, the motor dyspraxias suffer from an identity crisis that leads to confusion for the general pediatrician. Terms including *developmental coordination disorder*, *clumsy child syndrome*, *global dyspraxia*, *limb apraxia or dyspraxia*, and *developmental dyspraxia* are frequently used to describe the same poorly understood disorder. Although not all limb dyspraxias involve a motor speech anomaly, speech delay is a common comorbidity. Given the high frequency of sensory issues and low tone among the children described in this VA cohort and the strikingly similar clinical phenotype in a subgroup of children both on and off the spectrum, these data suggest that this is a common yet uncharacterized syndrome and clearly more than just a "speech disorder." We point out that "apraxia" is a

symptom rather than a diagnosis. Although VA has been reported to exist in isolation, we speculate that a more comprehensive neurodevelopmental and metabolic evaluation in those children likely would reveal other comorbidities. VA is also known to occur in many conditions in addition to ASD, including cerebral palsy,¹¹⁸ Down syndrome,¹¹⁹ velocardiofacial syndrome,¹²⁰ and other neurological disorders, or can be a symptom of stroke,¹²¹ brain tumor,¹²² or focal seizures.¹²³⁻¹²⁵ This suggests shared mechanistic pathways manifesting in a similar phenotype that is common to a number of otherwise distinct genetic, metabolic, or neurological conditions. In our cohort of 187 patients, several children were ultimately diagnosed with significant medical conditions, including a brain tumor, Sanfilippo Syndrome, a mitochondrial disorder (Complex I), and Phelan-McDermid Syndrome, a genetic disorder caused by a microdeletion on chromosome 22.

The genetic association with the clinical apraxia phenotype we describe is of particular interest. Phelan-McDermid Syndrome is a rare but likely underdiagnosed genetic disorder associated with a wide severity spectrum of conditions that most often include absent to delayed speech, general hypotonia, global developmental delays, increased tolerance to pain, and autistic-like affect.¹²⁶⁻¹²⁸ Although profound mental retardation has been described as characteristic, it is likely that only the most severely affected children are screened by fluorescence in situ hybridization. None of the children with Phelan-McDermid Syndrome in our VA cohort carried an ASD diagnosis. Two children had global developmental delay, but the third child did not and demonstrated no evidence of cognitive delay. All 3 children responded well to PUFA + vitamin E. Very few children in our database were screened for this or other microdeletions, and although the denominator is not known, it is suspected to be low given the limited medical or genetic workup that is generally undertaken in children with VA. Given the association of this deletion with proteins encoded by genes that assemble glutamate receptors,¹²⁹ this observation may provide insight into novel pathways that may be impacted by PUFA or vitamin E bioavailability. This is of particular interest given the cytoprotective nature of vitamin E to attenuate glutamate neurotoxicity¹³⁰⁻¹³³ and may have implications for other neuropsychiatric disorders that involve altered glutamatergic neurotransmission including anxiety,¹³⁴⁻¹³⁶ depression,^{134,137,138} bipolar disorder,¹³⁸ obsessive-compulsive disorders,^{135,139} and ADHD.^{134,140}

Pediatricians need to recognize the early warning signs of apraxia (Table 1), consider screening for common metabolic and nutritional abnormalities associated with this syndrome (Tables 3 and 4), and initiate a referral to a knowledgeable developmental pediatrician or pediatric neurologist to obtain an accurate diagnosis. In order to gain greater insight into the etiology of the disorder, a laboratory analysis including a neurometabolic and genetic workup with possibly a referral to a metabolic or genetic specialist, particularly if a carnitine deficiency is identified, is recommended. Magnetic resonance imaging of the brain may be helpful but is not always sensitive enough to identify neurologic differences. Early referral to a state-run early intervention program for speech and occupational therapy for a child under 3 years of age or to the local school district

INFLAMMATION AND OXIDATIVE STRESS: PATHWAYS TO THE APRAXIA PHENOTYPE

In this hypothetical model, genetic susceptibility is present but does not automatically translate to disease. Rather, it creates a vulnerable state that can be influenced by many factors that impact the balance of systemic homeostasis. Some are protective; others increase the risk of developing symptoms. As the number of adverse risk factors, exposures, or triggers increase, one reaches a tipping point beyond which symptoms develop and a patient manifests the clinical phenotype. These risk factors begin in utero,¹⁴⁵ with patterns of maternal health and nutritional status posing as potential risk factors.¹⁴⁶

Maternal (and paternal) allergy is a significant risk factor for allergy in the child.^{147,148} Delivery by Caesarean section also can increase risk of allergy,¹⁴⁹⁻¹⁵¹ as normal gut microflora is not passed from mother to child. Breast-feeding may confer protection.¹⁵² Early or frequent antibiotic use,¹⁵³ whether in the mother or infant, also will alter the gut microflora, which has implications for long-term health.¹⁵⁴

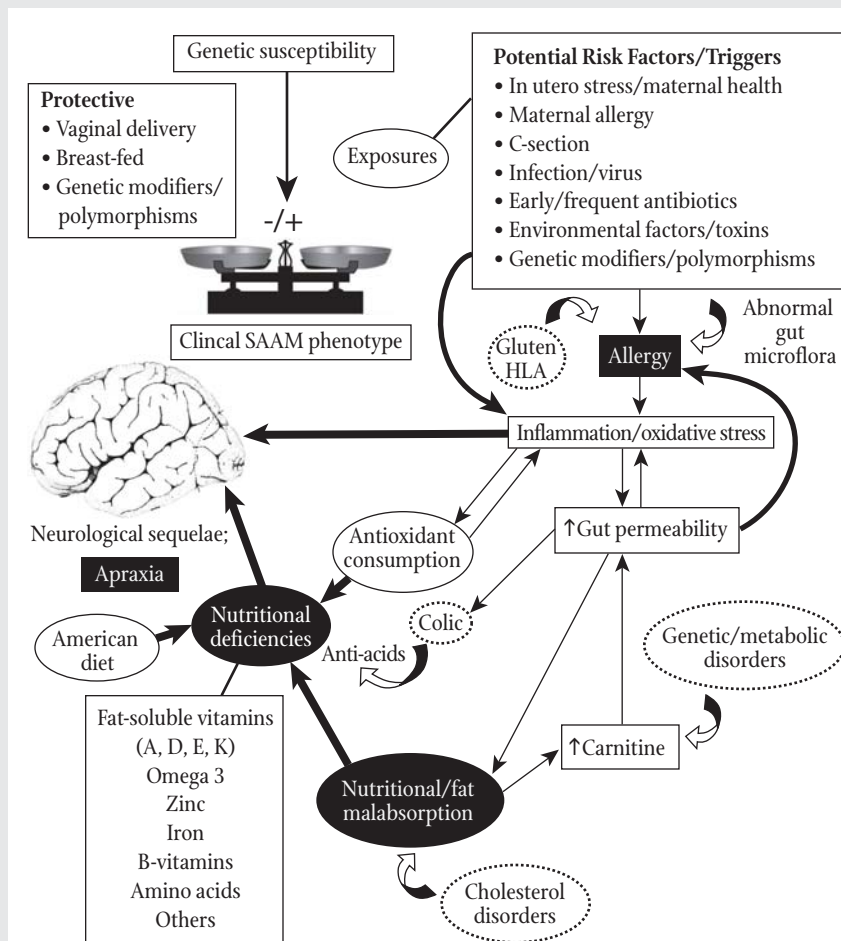
Other genetic modifiers also may influence the "protective-risk" balance scale. Carrying an HLA-DQ-1, 2 or 8 allele will increase susceptibility of an individual to develop gluten sensitivity,^{88,93,155,156} which may contribute to inflammation in the wheat-fed child. In

general, the atopic, allergic individual experiences excess inflammation and oxidative stress. Oxidative stress and inflammation consume antioxidants and micronutrients, leaving less available to counterbalance oxidative stress over time. The impact of abnormal gut flora and inflammation on the gastrointestinal (GI) tract may contribute to damage of the mucosal lining that leads to increased permeability or a "leaky gut,"^{157,158} which allows the abnormal passage of molecules from the GI tract into the bloodstream, triggers the development of multiple food allergies, and feeds the cycle of inflammation.^{159,162} Inflammation of the GI tract will also lead to malabsorption of key nutrients and fat, contributing to nutritional deficiencies that are compounded by a diet that may be lacking in high nutritional value, and rapid consumption of antioxidants in an environment of oxidative stress. A carnitine deficiency may be the result of malabsorption or the signal of a genetic, metabolic or mitochondrial disorder.^{76,80,81,99} Given its obligatory role in the maintenance of normal intestinal and colonic structure and function,⁹⁸ a carnitine deficiency will contribute to gut inflammation, villous atrophy, and malabsorption, fueling the cycle of oxidative stress. Regardless of the presence of obvious clinical symptoms of GI dysfunction, malabsorption will lead to a

variety of nutritional deficiencies, all of which will affect specific organ systems and health. Additional factors, like the frequent use of anti-acids and proton pump inhibitors in children with colic or recurrent GI symptoms may contribute to deficiencies like vitamin B₁₂,¹⁶³ which has neuropsychological and hematologic implications. Zinc is rapidly utilized in the inflammatory process.¹⁶⁴ A zinc deficiency may contribute to immune dysregulation and an increased susceptibility to infections¹⁶⁵ that lead to frequent antibiotic

usage. Inflammation also disrupts normal iron metabolism.¹⁶⁶ Low cholesterol levels may result from or contribute to fat malabsorption, depending on the underlying cause. However, low cholesterol bioavailability is not ideal for a child's developing brain.¹⁶⁷

Vitamin and nutrient deficiencies that result from inflammation, antioxidant consumption, and malabsorption are multiple and vary by individual, likely influenced by the status of the "protective-risk" balance scale. The impact of this cascade leads to a syndrome of allergy, apraxia, and malabsorption; however, there are many avenues along this pathway that a number of genotypically unique conditions may feed into and manifest in a similar clinical phenotype of apraxia. A milieu of inflammation and oxidative



stress will affect every cell it encounters. The polyunsaturated fatty acids in cell membranes are particularly vulnerable to lipid peroxidation and rapid destruction from oxidative stress, especially in cases of vitamin E deficiency.^{41,168} Key enzymes of metabolic pathways may malfunction as they oxidize, and transport of critical signaling molecules may be disrupted under the influence of oxidative stress and inflammation. A complex and multifactorial gamut of events, influenced by external forces of the "protective-risk" scale, may affect neurological function, motor planning, sensory interpretation, and muscle tone and evolve into an apraxia phenotype with a spectrum of severity.

Many aspects of this pathway can be targeted. Nutritional deficiencies can be screened for and reversed with supplementation, oxidative stress can be targeted with antioxidants, and inflammation can be modified pharmacologically and with dietary changes. Based on this model, apraxia is more likely a disorder that affects the brain and other organ systems rather than a primary disorder of the brain. The apraxic child needs speech and occupational therapy to treat the symptoms of this disorder; however, a "neuro-metabolic" approach that targets the underlying mechanisms will bring these children closer to recovery.

if the child is 3 or older is important for beginning the therapeutic process (although anecdotally, speech language pathologists in the private sector who specialize in motor speech disorders may be more knowledgeable about this disorder). Use of sign language should be recommended early on to encourage communication. Well-meaning reassurance that the late talker will catch up translates to missed opportunity for early intervention in the 25% of late talkers who have true pathology.²¹

Use of high-dose PUFA and vitamin E in children with a history of VA appeared to lead to rapid clinical improvement of many symptoms of this neurological condition in a large cohort. However, speech and coordination regressions described in some children when supplementation is stopped suggests abnormal fatty acid metabolism that is somehow compensated by super-physiologic doses of PUFAs and vitamin E. Several families have also reported transient losses of speech and coordination abilities during otherwise benign viral illnesses, suggesting that inflammation, regardless of the trigger, may compromise neurological function in these children. Elimination of a trigger of chronic inflammation through dietary restriction of gluten, dairy, yeast, or other individually specific food items also may explain benefits of special diets in the allergic child.

Many of our conclusions are speculative in the absence of controlled clinic trials. A better understanding of the underlying mechanisms accounting for these benefits is needed, and controlled research in apraxia and autism is warranted. The subjective nature of parental report and varied doses of supplements used are major limitations of this report. Future investigations should use validated and reliable outcome measures to determine the potential benefits of these nutritional interventions. Although this report lacks the rigor of prospective controlled research, the successful grassroots nature of this effort reflects an innovative Web-based approach to family-initiated research. There is potential for this to serve as a general model for biomedical researchers to interface with constructive ideas that emerge from patient-initiated research that might feed investigator-initiated research.

CONCLUSION

Oral, verbal, and limb apraxia are conditions that warrant more attention, independently and as part of the autism spectrum. Appropriate screening may identify a subgroup of children with a previously unrecognized syndrome of allergy, apraxia, and malabsorption who are responsive to nutritional interventions in addition to traditional speech and occupational therapy. Translational investigation of the mechanistic etiology of these motor planning disorders may lead to improved treatments, and addressing the metabolic and nutritional aberrations in these children may significantly improve their long-term outcome. In this era when research dollars are scarce, allocation of funds to study this rapidly growing problem among this generation's children may save millions of dollars in costs over time spent on early intervention programs that may become less necessary in a subgroup of children suffering from neurological complications associated with easily targeted nutritional deficiencies. Neurological sequelae of vitamin E deficiency become permanent

over time but are reversible if addressed early. PUFA⁴ and vitamin E supplementation are safe across a broad range of doses.^{37,141-144} As a benign intervention, it may be worthwhile for providers to consider a trial of empiric supplementation as a complementary approach to VA in addition to traditional speech and occupational therapy while we await the funding and results of clinical trials.

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