

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).<sup>1-16</sup> Studies demonstrating the importance of sufficient docosahexaenoic acid (DHA) for brain development<sup>17</sup> have led to the routine addition of DHA to most commercially available infant formulas. Supplementation with omega 3 fish oil is a safe intervention<sup>4,18</sup> that has led to improvements in behavior, motor skills, and language in many children affected by the aforementioned disabilities,<sup>2,4-6,9,10</sup> and recent placebo-controlled trials demonstrated benefits for children with autism<sup>19</sup> and ADHD.<sup>20</sup> 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.<sup>21</sup> Additionally, PUFA levels (DHA and EPA) are low in autism,<sup>11</sup> 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.<sup>22-24</sup> 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.<sup>25</sup>

VA is a neurologically based motor planning disorder of unknown etiology,<sup>26</sup> although there is evidence of genetic influences related to apraxia,<sup>27</sup> familial speech,<sup>28,29</sup> and neurologically based disorders such as dyslexia and ADHD.<sup>4,30,31</sup> 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,<sup>32</sup> 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.<sup>21</sup> Many children with VA present with homogeneous symptoms of neurological dysfunction that affect coordination, muscle tone, and sensory issues<sup>21,26,33</sup> in addition to expressive speech delay, suggesting a common underlying mechanism of disease. Vitamin E deficiency causes a constellation of symptoms<sup>34-37</sup> 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.<sup>1,3</sup> 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,<sup>4</sup> as doses of 1600 to 3200 IU/day are needed to reverse oxidative stress.<sup>5</sup> Even at 3200 IU/day, vitamin E clearly still works as an antioxidant rather than the theorized potential to become a pro-oxidant.<sup>5</sup> 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.<sup>6</sup> 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.

1. Hathcock JN, Azzi A, Blumberg J, et al. Vitamins E and C are safe across a broad range of intakes. *Am J Clin Nutr*. 2005;81(4):736-745.
2. Sokol RJ, Butler-Simon N, Conner C, et al. Multicenter trial of d-alpha-tocopheryl polyethylene glycol 1000 succinate for treatment of vitamin E deficiency in children with chronic cholestasis. *Gastroenterology*. 1993;104(6):1727-1235.
3. Traber MG. How much vitamin E? ... Just enough! *Am J Clin Nutr*. 2006;84(5):959-960.
4. Blumberg JB, Frei B. Why clinical trials of vitamin E and cardiovascular diseases may be fatally flawed. Commentary on "The relationship between dose of vitamin E and suppression of oxidative stress in humans". *Free Radic Biol Med*. 2007;43(10):1374-1376.
5. Roberts LJ 2nd, Oates JA, Linton MF, et al. The relationship between dose of vitamin E and suppression of oxidative stress in humans. *Free Radic Biol Med*. 2007;43(10):1388-1393.
6. Vitamin E. In: *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington, DC: National Academies Press; 2000:186-283.

**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.<sup>38-41</sup> 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	Chronic Cholestatic			Genetic Vitamin E Deficiency
	Abetalipo-proteinemia	Hepatobiliary Disease	Other Fat Malabsorption Disorders	
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 stress<sup>42-46</sup> may account for increased utilization of vitamin E and other fat-soluble vitamin deficiencies.<sup>12,47,48</sup> Children with ASD have evidence of global inflammation<sup>49,50</sup> and increased oxidative stress.<sup>7,51-55</sup> 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.<sup>42,43,56,57</sup> 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.<sup>58</sup> Inflammation of the GI tract,<sup>53-55,59-62</sup> food allergies, and gluten sensitivity<sup>47,54,63-67</sup> commonly found in apraxic and autistic children may further contribute to depletion of antioxidants and malabsorption of critical nutrients such as vitamin E<sup>65,68-73</sup> and carnitine,<sup>74-81</sup> 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,<sup>47,63,67</sup> conflicting reports are found in the literature.<sup>64</sup> Elevated plasma anti gliadin antibodies commonly found in ASD<sup>82-86</sup>

**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 B<sub>12</sub> bioavailability).
- Carnitine (total and free) and acyl-carnitine level
- Celiac panel (to include anti gliadin 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,<sup>86</sup> brain cells known to be damaged in ASD.<sup>51,87</sup> Alternatively, elevated anti gliadin antibodies may represent the signature of increased gut permeability and inflammation independent of celiac disease. Screening for anti gliadin 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 anti gliadin antibodies, remarkably higher than the 12% reported in the general population,<sup>88</sup> 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.<sup>65,88-91</sup> 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,<sup>91</sup> 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.<sup>92,93</sup>

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,<sup>94,95</sup> 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-tocopherol<sup>96</sup> is intriguing. Aberrations in such a transport system could plausibly result in an apraxia phenotype. Interestingly, clinical manifestations of Niemann-Pick C<sup>97</sup> 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 ASD<sup>77</sup> and is also a common feature of celiac disease.<sup>74-76,81</sup> 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.<sup>98</sup> However, low carnitine can be a clue to a number of metabolic disorders<sup>99</sup> and is associated with hypotonia.<sup>100</sup> More importantly, an untreated carnitine deficiency may adversely impact cardiac function and is associated with sudden death<sup>101-107</sup> and dilated cardiomyopathy.<sup>108-110</sup> 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.<sup>99</sup> 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.<sup>111</sup> Alpha-tocopherol transport protein has been identified in brain as well as liver.<sup>112,113</sup>

Like autism, cases of VA are also on the rise.<sup>114</sup> 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.<sup>115</sup> Early intervention with occupational therapy may improve outcome. Accumulating data clearly demonstrate that speech and coordination disorders go hand in hand.<sup>116,117</sup> 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,<sup>118</sup> Down syndrome,<sup>119</sup> velocardiofacial syndrome,<sup>120</sup> and other neurological disorders, or can be a symptom of stroke,<sup>121</sup> brain tumor,<sup>122</sup> or focal seizures.<sup>123-125</sup> 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.<sup>126-128</sup> 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,<sup>129</sup> 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 neurotoxicity<sup>130-133</sup> and may have implications for other neuropsychiatric disorders that involve altered glutamatergic neurotransmission including anxiety,<sup>134-136</sup> depression,<sup>134,137,138</sup> bipolar disorder,<sup>138</sup> obsessive-compulsive disorders,<sup>135,139</sup> and ADHD.<sup>134,140</sup>

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,<sup>145</sup> with patterns of maternal health and nutritional status posing as potential risk factors.<sup>146</sup> Maternal (and paternal) allergy is a significant risk factor for allergy in the child.<sup>147,148</sup> Delivery by Caesarean section also can increase risk of allergy,<sup>149-151</sup> as normal gut microflora is not passed from mother to child. Breast-feeding may confer protection.<sup>152</sup> Early or frequent antibiotic use,<sup>153</sup> whether in the mother or infant, also will alter the gut microflora, which has implications for long-term health.<sup>154</sup>

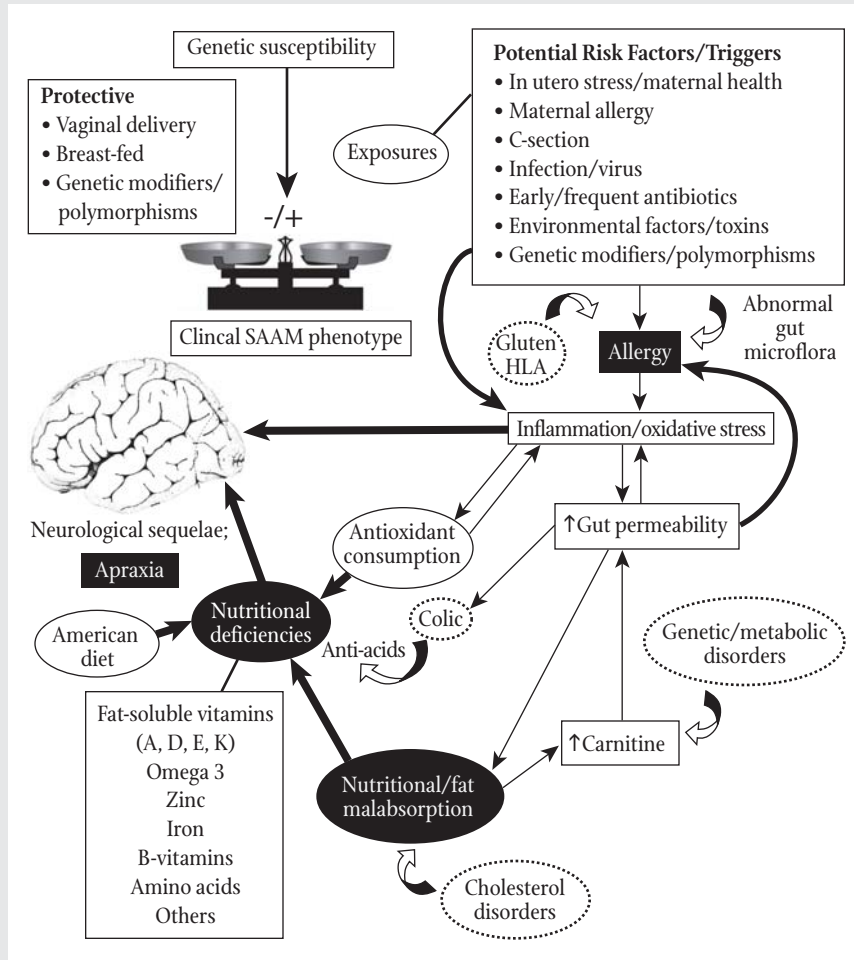
Other genetic modifiers also may influence the “protective-risk” balance scale. Carrying an HLA-DQ-1, 2 or 8 allele will increase susceptibility of an individual to develop gluten sensitivity,<sup>88,93,155,156</sup> which may contribute to inflammation in the wheat-fed child. In

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,”<sup>157,158</sup> 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.<sup>159,162</sup> 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.<sup>76,80,81,99</sup> Given its obligatory role in the maintenance of normal intestinal and colonic structure and function,<sup>98</sup> 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 B<sub>12</sub>,<sup>163</sup> which has neuropsychological and hematologic implications. Zinc is rapidly utilized in the inflammatory process.<sup>164</sup> A zinc deficiency may contribute to immune dysregulation and an increased susceptibility to infections<sup>165</sup> that lead to frequent antibiotic

usage. Inflammation also disrupts normal iron metabolism.<sup>166</sup> 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.<sup>167</sup>

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.<sup>41,168</sup> 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.<sup>21</sup>

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. PUFA<sup>4</sup> and vitamin E supplementation are safe across a broad range of doses.<sup>37,141-144</sup> 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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## REFERENCES

1. Cylharova E, Bell JG, Dick JR, Mackinlay EE, Stein JF, Richardson AJ. Membrane fatty acids, reading and spelling in dyslexic and non-dyslexic adults. *Eur Neuropsychopharmacol*. 2007;17(2):116-121.
2. Amminger GP, Berger GE, Schäfer MR, Klier C, Friedrich MH, Feucht M. Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study. *Biol Psychiatry*. 2007;61(4):551-553.
3. Sliwinski S, Croonenberghs J, Christophe A, Deboutte D, Maes M. Polyunsaturated fatty acids: do they have a role in the pathophysiology of autism? *Neuro Endocrinol Lett*. 2006;27(4):465-471.
4. Richardson AJ. Omega-3 fatty acids in ADHD and related neurodevelopmental disorders. *Int Rev Psychiatry*. 2006;18(2):155-172.
5. Young G, Conquer J. Omega-3 fatty acids and neuropsychiatric disorders. *Reprod Nutr Dev*. 2005;45(1):1-28.
6. Richardson AJ, Montgomery P. The Oxford-Durham study: a randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics*. 2004;115(5):1360-1366.
7. Clark-Taylor T, Clark-Taylor BE. Is autism a disorder of fatty acid metabolism? Possible dysfunction of mitochondrial beta-oxidation by long chain acyl-CoA dehydrogenase. *Med Hypotheses*. 2004;62(6):970-975.
8. Richardson AJ. Long-chain polyunsaturated fatty acids in childhood developmental and psychiatric disorders. *Lipids*. 2004;39(12):1215-1222.
9. Richardson AJ. Clinical trials of fatty acid treatment in ADHD, dyslexia, dyspraxia and the autistic spectrum. *Prostaglandins Leukot Essent Fatty Acids*. 2004;70(4):383-390.
10. Richardson AJ, Puri BK. A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26(2):233-239.
11. Vancassel S, Durand G, Barthélémy C, et al. Plasma fatty acid levels in autistic children. *Prostaglandins Leukot Essent Fatty Acids*. 2001;65(1):1-7.
12. Johnson S. Micronutrient accumulation and depletion in schizophrenia, epilepsy, autism and Parkinson's disease? *Med Hypotheses*. 2001;56(5):641-645.
13. Taylor KE, Richardson AJ. Visual function, fatty acids and dyslexia. *Prostaglandins Leukot Essent Fatty Acids*. 2000;63(1-2):89-93.
14. Richardson AJ, Puri BK. The potential role of fatty acids in attention-deficit/hyperactivity disorder. *Prostaglandins Leukot Essent Fatty Acids*. 2000;63(1-2):79-87.
15. Taylor KE, Higgins CJ, Calvin CM, et al. Dyslexia in adults is associated with clinical signs of fatty acid deficiency. *Prostaglandins Leukot Essent Fatty Acids*. 2000;63(1-2):75-78.
16. Richardson AJ, Ross MA. Fatty acid metabolism in neurodevelopmental disorder: a new perspective on associations between attention-deficit/hyperactivity disorder, dyslexia, dyspraxia and the autistic spectrum. *Prostaglandins Leukot Essent Fatty Acids*. 2000;63(1-2):1-9.
17. Gil A, Ramirez M, Gil M. Role of long-chain polyunsaturated fatty acids in infant nutrition. *Eur J Clin Nutr*. 2003;57 Suppl 1:S31-S34.
18. Uauy R, Hoffman DR, Birch EE, Birch DG, Jameson DM, Tyson J. Safety and efficacy of omega-3 fatty acids in the nutrition of very low birth weight infants: soy oil and marine oil supplementation of formula. *J Pediatr*. 1994;124(4):612-620.
19. Amminger GP, Berger GE, Schäfer MR, Klier C, Friedrich MH, Feucht M. Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study. *Biol Psychiatry*. 2007;61(4):551-553.
20. Sinn N, Bryan J, Wilson C. Cognitive effects of polyunsaturated fatty acids in children with attention deficit hyperactivity disorder symptoms: a randomised controlled trial. *Prostaglandins Leukot Essent Fatty Acids*. 2008;78(4-5):311-326.
21. Agin MC, Geng LF, Nicholl MJ. *The Late Talker: What to Do If Your Child Isn't Talking Yet*. New York, NY: St. Martin's Press; 2004.



22. Agin M. Verbal apraxia and the role of essential fatty acids: the perspective of a developmental pediatrician. Paper presented at: Research Workshop on Fatty Acids in Neurodevelopmental Disorders (FAND-2001), September 20-22, 2001; Oxford, UK.
23. Katz R, Agin M. Outcomes of essential fatty acid supplementation in verbal apraxia: an analysis of professional anecdotal reports. Paper presented at: Research Workshop on Fatty Acids in Neurodevelopmental Disorders (FAND-2001), September 20-22, 2002; Oxford, UK.
24. Katz R, Agin M. Outcomes of essential fatty acid supplementation in verbal apraxia. Paper presented at: 5th Congress of the International Society for the Study of Fatty Acids and Lipids, May 7-11, 2002; Montreal, Canada.
25. Roth LL. Essential fatty acid supplementation in verbal apraxia/dyspraxia: a time line of therapeutic outcomes in speech/communication. Paper presented at: Research Workshop on Fatty Acids in Neurodevelopmental Disorders (FAND-2001); 2001; Oxford, United Kingdom.
26. Kent RD. Research on speech motor control and its disorders: a review and prospective. *J Commun Disord.* 2000;33(5):391-427; quiz 428.
27. Lewis BA, Freebairn LA, Hansen A, Gerry Taylor H, Iyengar S, Shriberg LD. Family pedigrees of children with suspected childhood apraxia of speech. *J Commun Disord.* 2004;37(2):157-175.
28. Tomblin JB, Hafeman LL, O'Brien M. Autism and autism risk in siblings of children with specific language impairment. *Int J Lang Commun Disord.* 2003;38(3):235-250.
29. Spitz RV, Tallal P, Flax J, Benasich AA. Look who's talking: a prospective study of familial transmission of language impairments. *J Speech Lang Hear Res.* 1997;40(5):990-1001.
30. Stevenson J, Langley K, Pay H, et al. Attention deficit hyperactivity disorder with reading disabilities: preliminary genetic findings on the involvement of the ADRA2A gene. *J Child Psychol Psychiatry.* 2005;46(10):1081-1088.
31. Gilger JW, Pennington BF, DeFries JC. A twin study of the etiology of comorbidity: attention-deficit hyperactivity disorder and dyslexia. *J Am Acad Child Adolesc Psychiatry.* 1992;31(2):343-348.
32. Marilli KE, Adrianopoulos MV, Velleman SL, Foreman CG. Incidence of motor speech impairment in autism and Asperger's disorders. Poster presented at: American Speech-Language-Hearing Association Annual Convention; November 18, 2004; Pittsburgh, PA.
33. Nijland L, Maassen B, van der Meulen S. Evidence of motor programming deficits in children diagnosed with DAS. *J Speech Lang Hear Res.* 2003;46(2):437-450.
34. Sokol RJ. Vitamin E and neurologic deficits. *Adv Pediatr.* 1990;37:119-148.
35. Sokol RJ. Vitamin E and neurologic function in man. *Free Radic Biol Med.* 1989;6(2):189-207.
36. Traber MG, Packer L. Vitamin E: beyond antioxidant function. *Am J Clin Nutr.* 1995;62(6 Suppl):1501S-1509S.
37. Traber MG. How much vitamin E? . . . Just enough! *Am J Clin Nutr.* 2006;84(5):959-960.
38. Bourre JM. Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 1: micronutrients. *J Nutr Health Aging.* 2006;10(5):377-385.
39. Virmani A, Gaetani F, Binienda Z. Effects of metabolic modifiers such as carnitines, coenzyme Q10, and PUFAs against different forms of neurotoxic insults: metabolic inhibitors, MPTP, and methamphetamine. *Ann NY Acad Sci.* 2005 Aug;1053:183-191.
40. Nakamura MT, Cho HP, Xu J, Tang Z, Clarke SD. Metabolism and functions of highly unsaturated fatty acids: an update. *Lipids.* 2001;36(9):961-964.
41. Valk EE, Hornstra G. Relationship between vitamin E requirement and polyunsaturated fatty acid intake in man: a review. *Int J Vitam Nutr Res.* 2000;70(2):31-42.
42. Traber MG. Relationship of vitamin E metabolism and oxidation in exercising human subjects. *Br J Nutr.* 2006;96 Suppl 1:S34-S37.
43. Bruno RS, Traber MG. Vitamin E biokinetics, oxidative stress and cigarette smoking. *Pathophysiology.* 2006;13(3):143-149.
44. Brigelius-Flohé R, Traber MG. Vitamin E: function and metabolism. *FASEB J.* 1999;13(10):1145-1155.
45. Traber MG. Vitamin E, oxidative stress and "healthy ageing." *Eur J Clin Invest.* 1997;27(10):822-824.
46. Traber MG. Vitamin E. In: Shils ME, Olson JA, eds. *Modern Nutrition in Health and Disease.* 9th ed. Baltimore, MD: Williams and Wilkins; 1999:347-362.
47. Cornish E. Gluten and casein free diets in autism: a study of the effects on food choice and nutrition. *J Hum Nutr Diet.* 2002;15(4):261-269.
48. Clark JH, Rhoden DK, Turner DS. Symptomatic vitamin A and D deficiencies in an eight-year-old with autism. *JPEN J Parenter Enteral Nutr.* 1993;17(3):284-286.
49. Zimmerman AW, Jyonouchi H, Comi AM, et al. Cerebrospinal fluid and serum markers of inflammation in autism. *Pediatr Neurol.* 2005;33(3):195-201.
50. Becker KG. Autism, asthma, inflammation, and the hygiene hypothesis. *Med Hypotheses.* 2007;69(4):731-740.
51. Kern JK, Jones AM. Evidence of toxicity, oxidative stress, and neuronal insult in autism. *J Toxicol Environ Health B Crit Rev.* 2006;9(6):485-499.
52. Chauhan A, Chauhan V. Oxidative stress in autism. *Pathophysiology.* 2006;13(3):171-181.
53. Jyonouchi H, Geng L, Ruby A, Zimmerman-Bier B. Dysregulated innate immune responses in young children with autism spectrum disorders: their relationship to gastrointestinal symptoms and dietary intervention. *Neuropsychobiology.* 2005;51(2):77-85.
54. Ashwood P, Anthony A, Torrente F, Wakefield AJ. Spontaneous mucosal lymphocyte cytokine profiles in children with autism and gastrointestinal symptoms: mucosal immune activation and reduced counter regulatory interleukin-10. *J Clin Immunol.* 2004;24(6):664-673.
55. Black C, Kaye JA, Jick H. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database. *BMJ.* 2002;325(7361):419-421.
56. Traber MG. Vitamin E regulation. *Curr Opin Gastroenterol.* 2005;21(2):223-227.
57. Kaempf-Rotzoll DE, Traber MG, Arai H. Vitamin E and transfer proteins. *Curr Opin Lipidol.* 2003;14(3):249-254.
58. Ming X, Cheh MA, Yochum CL, Halladay AK, Wagner GC. Evidence of oxidative stress in autism derived from animal models. *Am J Biochem Biotechnol.* 2008;4(2):218-225.
59. Erickson CA, Stigler KA, Corkins MR, Posey DJ, Fitzgerald JF, McDougle CJ. Gastrointestinal factors in autistic disorder: a critical review. *J Autism Dev Disord.* 2005;35(6):713-727.
60. White JF. Intestinal pathophysiology in autism. *Exp Biol Med (Maywood).* 2003;228(6):639-649.
61. Wakefield AJ, Puleston JM, Montgomery SM, Anthony A, O'Leary JJ, Murch SH. Review article: the concept of entero-colonic encephalopathy, autism and opioid receptor ligands. *Aliment Pharmacol Ther.* 2002;16(4):663-674.
62. D'Eufemia P, Celli M, Finocchiaro R, et al. Abnormal intestinal permeability in children with autism. *Acta Paediatr.* 1996;85(9):1076-1079.
63. Christison GW, Ivany K. Elimination diets in autism spectrum disorders: any wheat amidst the chaff? *J Dev Behav Pediatr.* 2006;27(2 Suppl):S162-S171.
64. Elder JH, Shankar M, Shuster J, Theriaque D, Burns S, Sherrill L. The gluten-free, casein-free diet in autism: results of a preliminary double blind clinical trial. *J Autism Dev Disord.* 2006;36(3):413-420.
65. Bushara KO. Neurologic presentation of celiac disease. *Gastroenterology.* 2005;128(4 Suppl 1):S92-S97.
66. Shattock P, Whiteley P. Biochemical aspects in autism spectrum disorders: updating the opioid-excess theory and presenting new opportunities for biomedical intervention. *Expert Opin Ther Targets.* 2002;6(2):175-183.
67. Ashkenazi A, Levin S, Krasilovsky D. Gluten and autism. *Lancet.* 1980;1(8160):157.
68. Halfdanarson TR, Litzow MR, Murray JA. Hematological manifestations of celiac disease. *Blood.* 2007;109(2):412-421.
69. Hozyasz KK. Neurological manifestations in celiacs and vitamin E status. *Arq Neuropsiquiatr.* 2005;63(2A):371; author reply 371-372.
70. Kleopa KA, Kyriacou K, Zamba-Papanicolaou E, Kyriakides T. Reversible inflammatory and vacuolar myopathy with vitamin E deficiency in celiac disease. *Muscle Nerve.* 2005;31(2):260-265.
71. Hozyasz KK, Chelchowska M, Laskowska-Klita T. Vitamin E levels in patients with celiac disease [article in Polish]. *Med Wieku Rozwoj.* 2003;7(4 Pt 2):593-604.
72. Hallert C, Grant C, Grehn S, et al. Evidence of poor vitamin status in coeliac patients on a gluten-free diet for 10 years. *Aliment Pharmacol Ther.* 2002;16(7):1333-1339.
73. Gordon N. Cerebellar ataxia and gluten sensitivity: a rare but possible cause of ataxia, even in childhood. *Dev Med Child Neurol.* 2000;42(4):283-286.
74. Karakoç E, Erdem S, Sökmensüer C, Kansu T. Encephalopathy due to carnitine deficiency in an adult patient with gluten enteropathy. *Clin Neurol Neurosurg.* 2006;108(8):794-797.
75. Curione M, Danese C, Viola F, et al. Carnitine deficiency in patients with coeliac disease and idiopathic dilated cardiomyopathy. *Nutr Metab Cardiovasc Dis.* 2005;15(4):279-283.
76. Hozyasz KK, Czerwinska B. Free and total carnitine levels in patients with celiac disease. *Indian J Gastroenterol.* 2004;23(5):194.
77. Filipek PA, Juranek J, Nguyen MT, Cummings C, Gargus JJ. Relative carnitine deficiency in autism. *J Autism Dev Disord.* 2004;34(6):615-623.
78. Fitzgerald JF, Troncone R, Roggero P, et al. Clinical quiz. Secondary carnitine deficiency due to celiac disease. *J Pediatr Gastroenterol Nutr.* 2003;36(5):636, 646.
79. Lombard J. Autism: a mitochondrial disorder? *Med Hypotheses.* 1998;50(6):497-500.
80. Pons R, De Vivo DC. Primary and secondary carnitine deficiency syndromes. *J Child Neurol.* 1995;10 Suppl 2:S8-S24.
81. Lerner A, Gruener N, Iancu TC. Serum carnitine concentrations in coeliac disease. *Gut.* 1993;34(7):933-935.
82. Margutti P, Delunardo F, Ortona E. Autoantibodies associated with psychiatric disorders. *Curr Neurovasc Res.* 2006;3(2):149-157.
83. Pavone L, Fiumara A, Bottaro G, Mazzone D, Coleman M. Autism and celiac disease: failure to validate the hypothesis that a link might exist. *Biol Psychiatry.* 1997;42(1):72-75.
84. Walker-Smith J, Andrews J. Alpha-1-antitrypsin, autism, and coeliac disease. *Lancet.* 1972;2(7782):883-884.
85. Vojdani A, Bazargan M, Vojdani E, et al. Heat shock protein and gliadin peptide promote development of peptidase antibodies in children with autism and patients with autoimmune disease. *Clin Diagn Lab Immunol.* 2004;11(3):515-524.
86. Vojdani A, O'Bryan T, Green JA, et al. Immune response to dietary proteins, gliadin and cerebellar peptides in children with autism. *Nutr Neurosci.* 2004;7(3):151-161.
87. Kern JK. Purkinje cell vulnerability and autism: a possible etiological connection. *Brain Dev.* 2003;25(6):377-382.
88. Hadjivassiliou M, Grünewald RA, Kandler RH, et al. Neuropathy associated with gluten sensitivity. *J Neurol Neurosurg Psychiatry.* 2006;77(11):1262-1266.
89. Simonati A, Battistella PA, Guariso G, Clementi M, Rizzuto N. Coeliac disease associated with peripheral neuropathy in a child: a case report. *Neuropediatrics.* 1998;29(3):155-158.
90. Hadjivassiliou M, Chattopadhyay AK, Davies-Jones GA, Gibson A, Grünewald RA, Lobo AJ. Neuromuscular disorder as a presenting feature of coeliac disease. *J Neurol Neurosurg Psychiatry.* 1997;63(6):770-775.
91. Hadjivassiliou M, Grünewald RA, Davies-Jones GA. Gluten sensitivity as a neurological illness. *J Neurol Neurosurg Psychiatry.* 2002;72(5):560-563.
92. Fine KD, Do K, Schulte K, et al. High prevalence of celiac sprue-like HLA-DQ genes and enteropathy in patients with the microscopic colitis syndrome. *Am J Gastroenterol.* 2000;95(8):1974-1982.
93. Hadjivassiliou M, Grünewald R, Sharrack B, et al. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain.* 2003;126(Pt 3):685-691.
94. Tierney E, Bukelis I, Thompson RE, et al. Abnormalities of cholesterol metabolism in autism spectrum disorders. *Am J Med Genet B Neuropsychiatr Genet.* 2006;141B(6):666-668.
95. Bukelis I, Porter FD, Zimmerman AW, Tierney E. Smith-Lemli-Opitz syndrome and autism spectrum disorder. *Am J Psychiatry.* 2007;164(11):1655-1661.

96. Narushima K, Takada T, Yamanashi Y, Suzuki H. Niemann-pick C1-like 1 mediates alpha-tocopherol transport. *Mol Pharmacol*. 2008;74(1):42-49.
97. Garver WS, Francis GA, Jelinek D, et al. The National Niemann-Pick C1 disease database: report of clinical features and health problems. *Am J Med Genet A*. 2007;143A(11):1204-1211.
98. Shekhawat PS, Srinivas SR, Matern D, et al. Spontaneous development of intestinal and colonic atrophy and inflammation in the carnitine-deficient jvs (OCTN2(-/-)) mice. *Mol Genet Metab*. 2007;92(4):315-324.
99. Stanley CA. Carnitine deficiency disorders in children. *Ann N Y Acad Sci*. 2004 Nov;1033:42-51.
100. Pons R, Carozzo R, Tein I, et al. Deficient muscle carnitine transport in primary carnitine deficiency. *Pediatr Res*. 1997;42(5):583-587.
101. Rinaldo P, Stanley CA, Hsu BY, Sanchez LA, Stern HJ. Sudden neonatal death in carnitine transporter deficiency. *J Pediatr*. 1997;131(2):304-305.
102. Okamoto M, Ueno Y. Is sudden death with vitamin C deficiency caused by lack of carnitine? *J Clin Forensic Med*. 2006;13(1):26-29.
103. Melegh B, Bene J, Mogyorósy G, et al. Phenotypic manifestations of the OCTN2 V295X mutation: sudden infant death and carnitine-responsive cardiomyopathy in Roma families. *Am J Med Genet A*. 2004;131(2):121-126.
104. Legge M. Systemic carnitine deficiency as the cause of a prolonged illness and sudden death in a six-year-old child. *J Inheri Metab Dis*. 1985;8(3):159.
105. Harpey JP, Charpentier C, Coudé M, Divry P, Paturneau-Jouas M. Sudden infant death syndrome and multiple acyl-coenzyme A dehydrogenase deficiency, ethylmalonic-adipic aciduria, or systemic carnitine deficiency. *J Pediatr*. 1987;110(6):881-884.
106. Guideri F, Acampa M, Hayek Y, Zappella M. Effects of acetyl-L-carnitine on cardiac dysautonomia in Rett syndrome: prevention of sudden death? *Pediatr Cardiol*. 2005;26(5):574-577.
107. Chalmers RA, Stanley CA, English N, Wigglesworth JS. Mitochondrial carnitine-acylcarnitine translocase deficiency presenting as sudden neonatal death. *J Pediatr*. 1997;131(2):220-225.
108. Zales VR, Benson DW Jr. Reversible cardiomyopathy due to carnitine deficiency from renal tubular wasting. *Pediatr Cardiol*. 1995;16(2):76-78.
109. Takahashi R, Okumura K, Asai T, et al. Dietary fish oil attenuates cardiac hypertrophy in lipotoxic cardiomyopathy due to systemic carnitine deficiency. *Cardiovasc Res*. 2005;68(2):213-223.
110. Paulson DJ. Carnitine deficiency-induced cardiomyopathy. *Mol Cell Biochem*. 1998;180(1-2):33-41.
111. Sokol RJ. Vitamin E deficiency and neurological disorders. In: Packer L, Fuchs J, eds. *Vitamin E in Health and Disease: Biochemistry and Clinical Applications*. New York: Marel Dekker; 1993:815-849.
112. Hosomi A, Goto K, Kondo H, et al. Localization of alpha-tocopherol transfer protein in rat brain. *Neurosci Lett*. 1998;256(3):159-162.
113. Copp RP, Wisniewski T, Hentati F, Larnaout A, Ben Hamida M, Kayden HJ. Localization of alpha-tocopherol transfer protein in the brains of patients with ataxia with vitamin E deficiency and other oxidative stress related neurodegenerative disorders. *Brain Res*. 1999;822(1-2):80-87.
114. No authors listed. Childhood apraxia of speech cases on the rise. *Science Daily*. October 30, 2007. Available at: <http://www.sciencedaily.com/releases/2007/10/071029133114.htm>. Accessed February 5, 2008.
115. Gaines R, Missiuna C. Early identification: are speech/language-impaired toddlers at increased risk for Developmental Coordination Disorder? *Child Care Health Dev*. 2007;33(3):325-332.
116. Newmeyer AJ, Grether S, Grasha C, et al. Fine motor function and oral-motor imitation skills in preschool-age children with speech-sound disorders. *Clin Pediatr (Phila)*. 2007;46(7):604-611.
117. Rapin I, ed. *Preschool Children with Inadequate Communication: Developmental Language Disorder, Autism, Low IQ: Clinics in Developmental Medicine*, No. 139. London: Mac Keith Press; 1996.
118. Pirla S, van der Meere J, Pentikainen T, et al. Language and motor speech skills in children with cerebral palsy. *J Commun Disord*. 2007;40(2):116-128.
119. Dodd B, Thompson L. Speech disorder in children with Down's syndrome. *J Intellect Disabil Res*. 2001;45(Pt 4):308-316.
120. Kummer AW, Lee L, Stutz LS, Maroney A, Brandt JW. The prevalence of apraxia characteristics in patients with velocardiofacial syndrome as compared with other cleft populations. *Cleft Palate Craniofac J*. 2007;44(2):175-181.
121. West C, Hesketh A, Vail A, Bowen A. Interventions for apraxia of speech following stroke. *Cochrane Database Syst Rev*. 2005;(4):CD004298.
122. Strange P, Wohlert L. Primary brain stem tumours. *Acta Neurochir (Wien)*. 1982;62(3-4):219-232.
123. Rausch R, MacDonald K. Effects of hemisphere speech dominance and seizure focus on patterns of behavioral response errors for three types of stimuli. *Brain Cogn*. 1997;33(2):161-177.
124. Koerner M, Laxer KD. Ictal speech, postictal language dysfunction, and seizure lateralization. *Neurology*. 1988;38(4):634-636.
125. Kobayashi M, Takayama H, Mihara B, Sugishita M. Partial seizure with aphasic speech arrest caused by watching a popular animated TV program. *Epilepsia*. 1999;40(5):652-654.
126. Cusmano-Ozog K, Manning MA, Hoyne HE. 22q13.3 deletion syndrome: a recognizable malformation syndrome associated with marked speech and language delay. *Am J Med Genet C Semin Med Genet*. 2007;145C(4):393-398.
127. Phelan MC. Deletion 22q13.3 syndrome. *Orphanet J Rare Dis*. 2008 May 27;3:14.
128. Philippe A, Boddaert N, Vaire-Douret L, et al. Neurobehavioral profile and brain imaging study of the 22q13.3 deletion syndrome in childhood. *Pediatrics*. 2008;122(2):e376-e382.
129. Roussignol G, Ango F, Romorini S, et al. Shank expression is sufficient to induce functional dendritic spine synapses in aspiny neurons. *J Neurosci*. 2005;25(14):3560-3570.
130. Schubert D, Piasecki D. Oxidative glutamate toxicity can be a component of the excitotoxicity cascade. *J Neurosci*. 2001;21(19):7455-7462.
131. Schubert D, Kimura H, Maher P. Growth factors and vitamin E modify neuronal glutamate toxicity. *Proc Natl Acad Sci U S A*. 1992;89(17):8264-8267.
132. Barger SW, Goodwin ME, Porter MM, Beggs ML. Glutamate release from activated microglia requires the oxidative burst and lipid peroxidation. *J Neurochem*. 2007;101(5):1205-1213.
133. al-Shabanah OA, Mostafa YH, Hassan MT, Khairaldin AA, al-Sawaf HA. Vitamin E protects against bacterial endotoxin-induced increase of plasma corticosterone and brain glutamate in the rat. *Res Commun Mol Pathol Pharmacol*. 1996;92(1):95-105.
134. Howells FM, Russell VA. Glutamate-stimulated release of norepinephrine in hippocampal slices of animal models of attention-deficit/hyperactivity disorder (spontaneously hypertensive rat) and depression/anxiety-like behaviours (Wistar-Kyoto rat). *Brain Res*. 2008 Mar 20;1200:107-115.
135. Cortese BM, Phan KL. The role of glutamate in anxiety and related disorders. *CNS Spectr*. 2005;10(10):820-830.
136. Bergink V, van Megen HJ, Westenberg HG. Glutamate and anxiety. *Eur Neuropsychopharmacol*. 2004;14(3):175-183.
137. McNally L, Bhagwagar Z, Hannestad J. Inflammation, glutamate, and glia in depression: a literature review. *CNS Spectr*. 2008;13(6):501-510.
138. Hashimoto K, Sawa A, Iyo M. Increased levels of glutamate in brains from patients with mood disorders. *Biol Psychiatry*. 2007;62(11):1310-1316.
139. Chakrabarty K, Bhattacharyya S, Christopher R, Khanna S. Glutamatergic dysfunction in OCD. *Neuropsychopharmacology*. 2005;30(9):1735-1740.
140. Courvoisier H, Hooper SR, Fine C, Kwock L, Castillo M. Neurometabolic functioning and neuropsychological correlates in children with ADHD-H: preliminary findings. *J Neuropsychiatry Clin Neurosci*. 2004;16(1):63-69.
141. Hathcock JN, Azzì A, Blumberg J, et al. Vitamins E and C are safe across a broad range of intakes. *Am J Clin Nutr*. 2005;81(4):736-745.
142. Sokol RJ, Butler-Simon N, Conner C, et al. Multicenter trial of d-alpha-tocopheryl polyethylene glycol 1000 succinate for treatment of vitamin E deficiency in children with chronic cholestasis. *Gastroenterology*. 1993;104(6):1727-1735.
143. Roberts LJ 2nd, Oates JA, Linton MF, et al. The relationship between dose of vitamin E and suppression of oxidative stress in humans. *Free Radic Biol Med*. 2007;43(10):1388-1393.
144. Blumberg JB, Frei B. Why clinical trials of vitamin E and cardiovascular diseases may be fatally flawed. Commentary on "The relationship between dose of vitamin E and suppression of oxidative stress in humans". *Free Radic Biol Med*. 2007;43(10):1374-1376.
145. Cunningham-Rundles S, McNeely DF, Moon A. Mechanisms of nutrient modulation of the immune response. *J Allergy Clin Immunol*. 2005;115(6):1119-1128; quiz 1129.
146. Kaza U, Knight AK, Bahna SL. Risk factors for the development of food allergy. *Curr Allergy Asthma Rep*. 2007;7(3):182-186.
147. Haddeland U, Brandtzaeg P, Nakstad B. Maternal allergy influences the proliferation of neonatal T cells expressing CCR4, CXCR5 or CD103. *Clin Exp Allergy*. 2007;37(6):856-864.
148. Ashad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. *Chest*. 2005;127(2):502-508.
149. Pistiner M, Gold DR, Abdulkherim H, Hoffman E, Celedón JC. Birth by cesarean section, allergic rhinitis, and allergic sensitization among children with a parental history of atopy. *J Allergy Clin Immunol*. 2008;122(2):274-279.
150. Tollán MC, Moster D, Daltveit AK, Irgens LM. Cesarean section and risk of severe childhood asthma: a population-based cohort study. *J Pediatr*. 2008;153(1):112-116.
151. Eggesbo M, Botten G, Stigum H, Nafstad P, Magnus P. Is delivery by cesarean section a risk factor for food allergy? *J Allergy Clin Immunol*. 2003;112(2):420-426.
152. Ehlhlay MS, Bener A. Duration of breast-feeding and the risk of childhood allergic diseases in a developing country. *Allergy Asthma Proc*. 2008;29(4):386-391.
153. Alm B, Erdes L, Möllborg P, et al. Neonatal antibiotic treatment is a risk factor for early wheezing. *Pediatrics*. 2008;121(4):697-702.
154. Calder PC, Krauss-Etschmann S, de Jong EC, et al. Early nutrition and immunity—progress and perspectives. *Br J Nutr*. 2006;96(4):774-790.
155. Wright DH. The major complications of coeliac disease. *Baillieres Clin Gastroenterol*. 1995;9(2):351-369.
156. Kaukinen K, Partanen J, Mäki M, Collin P. HLA-DQ typing in the diagnosis of celiac disease. *Am J Gastroenterol*. 2002;97(3):695-699.
157. Liu Z, Li N, Neu J. Tight junctions, leaky intestines, and pediatric diseases. *Acta Paediatr*. 2005;94(4):386-393.
158. Fasano A, Shea-Donohue T. Mechanisms of disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases. *Nat Clin Pract Gastroenterol Hepatol*. 2005;2(9):416-422.
159. Macdonald TT, Monteleone G. Immunity, inflammation, and allergy in the gut. *Science*. 2005;307(5717):1920-1925.
160. Heyman M. Gut barrier dysfunction in food allergy. *Eur J Gastroenterol Hepatol*. 2005;17(12):1279-1285.
161. Laitinen K, Isolauri E. Management of food allergy: vitamins, fatty acids or probiotics? *Eur J Gastroenterol Hepatol*. 2005;17(12):1305-1311.
162. Landgraf MA, Landgraf RG, Carvalho MH, Fortes ZB. Modulation of lung allergic inflammation and malnutrition. *Neuroimmunomodulation*. 2008;15(3):194-206.
163. Oh R, Brown DL. Vitamin B12 deficiency. *Am Fam Physician*. 2003;67(5):979-986.
164. Vasto S, Mocchegiani E, Malavolta M, et al. Zinc and inflammatory/immune response in aging. *Ann N Y Acad Sci*. 2007 Apr;1100:111-122.
165. Fischer Walker C, Black RE. Zinc and the risk for infectious disease. *Annu Rev Nutr*. 2004;24:255-275.
166. Ganz T. Hepsidin, a key regulator of iron metabolism and mediator of anemia of inflammation. *Blood*. 2003;102(3):783-788.
167. Kelley RI. Inborn errors of cholesterol biosynthesis. *Adv Pediatr*. 2000;47:1-53.
168. Turchetto E, Pignatti C. Protection of essential fatty acids by vitamin E [article in Italian]. *Acta Vitaminol Enzymol*. 1982;4(3):267-277.