CASE REPORT

Autism Spectrum Disorders

自闭症谱系障碍

Trastornos del espectro autista

Kara Fitzgerald, ND; Mark Hyman, MD; Case Clinicians: Mark Hyman, MD; Kathie Swift, MS, RD

Author Affiliations
Kara Fitzgerald, ND, is coauthor of *Case Studies in Integrative and Functional Medicine* and is on faculty for the Institute for Functional Medicine, Gig Harbor, Washington. Mark Hyman, MD, is chairman of the Institute for Functional Medicine. Kathie Swift, MS, RD, is the senior nutrition advisor for the Optimal Health and Prevention Research Foundation in San Diego, California. She also practices at the UltraWellness Center, in Lenox, Massachusetts, and the Kripalu Center for Yoga and Health, in Stockbridge, Massachusetts, and is an instructor in the country's first graduate program in Mind Body Medicine at Saybrook University, San Francisco, California.

Correspondence
Kara Fitzgerald, ND
info@drkarafitzgerald.com

Citation
Global Adv Health Med. 2012;1(4):62-74.

Key Words
Autism spectrum disorders, irritability, food reactions, developmental disorder

ABSTRACT

Autism spectrum disorders (ASDs) are collectively the most commonly diagnosed pediatric neurodevelopmental condition. ASDs include autism, pervasive developmental disorder-not otherwise specified (PDD-NOS), Rett syndrome and Asperger disorder. ASD is characterized by impaired communication and social interaction and may involve developmental delays and seizure disorders. Recent parent-reported diagnosis of ASD in the United States put it at higher levels (1:91) than previously thought, with its diagnosis in boys occurring 4 to 5 times more frequently than in girls (1:58).[1] CDC estimates are currently 1:110;[1] up from 1:150 in 2007.[2] Annual medical expenditures for those affected are generally four to six times greater than for those without ASD.[1] While twin studies demonstrate that genetics play a significant role in ASD, the impact of environment should not be underestimated, given the approximate 20-fold increase in incidence over the last 20 years.[3]

简介

自闭症谱系障碍（Autism spectrum disorders，ASD）是最常见的小儿神经发育疾病。ASD 包括自闭症、广泛性发育障碍 – 不另行举例 （PDD–NOS）、雷特综合征和亚氏保加症。ASD 的病征包括沟通和社交互动障碍，并可能伴有发育迟缓和癫痫发作。近期，美国境内由父母报告的 ASD 诊断病例上升至更高水平 （1:91），高于先前估计，男孩的诊断病例通常比女孩 （1:58） 多 4 到 5 倍。[1] CDC 估计量目前为 1:110；比 2007 年的 1:150 提高 [1]。[2] 治疗此类患者的年度医疗开支比未患有 ASD 的患者高出 4 到 6 倍。1 虽然孪生儿童研究表明基因对 ASD 起重要作用，但是，考虑到过去 20 年中疾病发生率增加大约 20 倍，环境的影响不应被低估。[3]

SINOPSIS

Los trastornos del espectro autista (TEA) son, en su conjunto, una de las enfermedades pediátricas del desarrollo neurológico diagnosticadas con más frecuencia. Los TEA incluyen el autismo, el trastorno generalizado del desarrollo no especificado (TGD-NE), el síndrome de Rett y el síndrome de Asperger. Los TEA se caracterizan por los problemas de comunicación y de interacción social y pueden incluir retrasos del desarrollo y trastornos convulsivos. Según la información aportada recientemente por progenitores en relación con el diagnóstico de TEA en Estados Unidos, el diagnóstico de TEA se sitúa en niveles superiores (1:91) de lo que se creía previamente; el diagnóstico en varones es de 4 a 5 veces más frecuente que en mujeres (1:58).[1] Los CDC calculan que en la actualidad es de 1:110;1 hasta 1:150 en 2007.[2] Los gastos médicos anuales de los afectados son, por lo general, de cuatro a seis veces superiores a los de los que no padecen TEA.1 Mientras que estudios en gemelos muestran que la genética desempeña un papel fundamental en los TEA, el efecto del entorno no debe infravalorarse, dado el aumento de la incidencia, que aproximadamente se ha multiplicado por 20 a lo largo de los últimos 20 años.[3]

CASE HISTORY

TL was 2.5 years old when he presented with a recent diagnosis of regressive pervasive developmental disorder-not otherwise specified (PDD-NOS; Table 1). PDD-NOS falls into the autistic spectrum of disorders (ASD) and is sometimes referred to as atypical autism. According to his parents, TL's symptoms began at age 22 months, shortly after receiving the measles, mumps, and rubella (MMR) vaccine. TL was previously meeting normal developmental milestones and had a vocabulary of 20 words. He was a happy and responsive baby who smiled regularly. Over the months since the vaccine, TL had developed aphasia, was irritable and intolerant of certain sensory stimuli, and had difficulty maintaining eye contact, interacting with others, or responding to his name. He developed foul-smelling bowel movements (BMs), itchy ears, dark circles under his eyes, and red blotchy skin. He refused all but soft-textured foods.

Comprehensive neuropsychiatric and developmental evaluations were conducted (listed below). Based on the results, full-time special education with speech and occupational therapy was recommended.

While pregnant with TL, his mother consumed tuna regularly and had two amalgams. They lived in a large east coast city, in an apartment building known to have lead paint. The building also required periodic insect exterminations, although never in the family's own unit.

TL's delivery was by emergency cesarean section at 36 weeks because of placental abruption. His birth weight was 6 lbs, 10 oz, and his Apgar score was normal.

Table 1 2.5-Year-Old Male With Pervasive Developmental Disorder

Additional Symptoms and Conditions	Irritable bowel syndrome, irritability, skin rash
Tests used	Complete blood count and metabolic panel, food-specific IgE and IgG antibodies, multiprofile panel (fatty acids, amino acids, organic acids, essential and toxic elements, lipid-soluble vitamins, and oxidative stress markers), functional stool test, celiac panel, genetic testing, urinary polypeptides, urine toxic elements test
Imbalances identified	Lactic acidosis, bacterial and fungal dysbiosis, GI inflammation, polypeptide elevations, anti-gliadin antibodies, IgG food reactions, intestinal hyperpermeability, fatty acid imbalance, oxidative stress, glutathione-s-transferase enzyme mutation, methylation and sulfuration lesions, subclinical mitochondropathy, essential element deficiencies
Treatments	High-dose probiotics, digestive enzyme, cod liver oil, multivitamin and mineral powder, zinc and magnesium, methylation support nutrients, rifaximin (Xifaxan), nystatin; gluten and dairy-free diet, avoid IgG sensitivities
Outcome	At 10 months, in mainstream nursery school, indistinguishable from the other children
Discussion/significance	This child's response to treatment, while remarkable, is not considered unusual among clinicians using what is described as a biomedical approach.[4-6] Given the rapidly rising incidence of this disorder,[3] research evaluating the efficacy of the biomedical approach to treating ASD is warranted.

TL was breastfed for 3 months until he developed colic with severe bloating. He was switched to Enfamil. It was later determined that he was dairy intolerant. Gerber rice cereal was introduced at 6 months, followed by Cheerios (indicating possible gluten exposure). TL suffered from frequent colds and diaper rash and had a month-long stomach virus invoking much vomiting and diarrhea. TL followed a full pediatric vaccine schedule and was reportedly irritable after receiving vaccines per administration.

TL's family was generally healthy, with no incidence of autism spectrum disorders, allergies, or autoimmune conditions.

TL's diet was limited, given his intolerance to many foods and food textures. He ate soy yogurt, berries, bananas, bread, rice, peanut butter, and limited fruits and vegetables.

Neuropsychiatric/Developmental Evaluations and Initial Laboratory Results

TL underwent multiple neuropsychiatric and developmental evaluations to achieve the diagnosis of PDD-NOS (Tables 2 and 3). Significant findings or pertinent negative findings are listed under each assessment tool.

- Gross motor development and tone
  - TL's gross motor development and proximal and distal extremity muscle tone were determined to be within normal limits.
- Hearing evaluation
  - TL's hearing evaluation was within normal limits.
- Bayley Scales of Infant Development II
  - Mental Development Index: < 50; (> -2.0 standard deviation points (SD) below the mean.)
- Vinland Adaptive Behavior Scales
  - Communication: 73 (moderately low)
  - Socialization: 74 (moderately low)
- Sensory Caregiver Profile 7 to 36 months
  - Oral sensory processing: > -2.0 SD below the mean
- Childhood Autism Rating Scale (CARS): 32
  - Comment: In the CARS assessment, TL showed significant delay in social and play skills, listening, visual response, object use and verbal and nonverbal communication. A score of 32 was consistent with Autistic/PDD-NOS disorders
- Peabody Developmental Scale II:
  - > 25% delay fine and visual motor skills

Laboratory tests ordered and rationale: It is believed by many clinicians and researchers that autism patho-

Table 2 Developmental Assessment of Young Children

Domain	TL's Percentile Ranking	Z-score
Cognitive development	6	–1.67
Communication development	0.3	–3.00
Motor development	23	–0.67
Social/Emotional development	9	–1.33
Adaptive skills	7	–1.33

Table 3 Preschool Language Scale-4

	Auditory Comprehension	Expressive Communication	Total Language
Percentile rank	1	3	1
Standard score	57	71	60
Standard deviation	> 2.5 SD below mean	2.0 SD below mean	> 2.5 SD below mean

genesis consists of a complex interplay between genetics (including polymorphisms in detoxification and biotransformation enzymes), environmental exposures and imbalanced immune response.[7] Significant food immunological reactions, gastrointestinal disturbances and nutrient imbalances are frequently found in ASD.[8] At the molecular level, oxidative stress, methylation lesions, inflammation and mitochondrial dysfunction are common findings.[9,10] Successful treatment generally requires addressing multiple imbalances simultaneously. Because of these factors, clinicians treating autistic individuals from a functional or integrative approach tend to use laboratory testing broadly, evaluating numerous areas of potential imbalance:

1. Complete blood count and metabolic panel: Routine laboratory assessments
2. Food-specific IgE and IgG antibodies: Food reactions are a common finding in ASD.[11]
3. Multiprofile panel: A comprehensive assessment including fatty acids, amino acids, organic acids, essential and toxic elements, lipid-soluble vitamins and oxidative stress markers; assists in detecting the individual etiopathogenic factors used to individualize treatment plans.
4. Stool test: Assessment of GI microbial status and GI function. GI imbalances are a common finding in many inflammatory conditions.[12]
5. Celiac panel: Gluten intolerance and gluten sensitivity have been found in ASD.[8,11,13-15]
6. Genetic testing for mutations in glutathione and methylation enzymes: Increased incidence of mutations in these enzyme systems has been identified in ASD.[16-18]
7. Urinary polypeptides: Elevation of specific polypeptides has been associated with ASD.[19]
8. Urine toxic elements test with DMPS provocation: Elevated toxic metals have been found in ASD.[20] Since the provocation agent may chelate essential as well as toxic elements, the test was to be completed after initial treatment had begun.

Only significant findings are discussed below:

Pertinent Negative Laboratory Results:

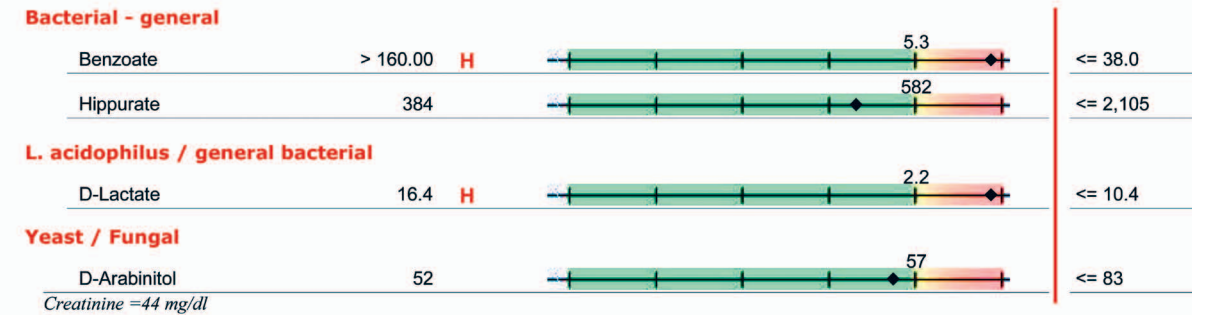

Figure 1 Urinary organic acids—compounds of bacterial and fungal origin. Elevations were consistent with bacterial overgrowth. The elevated benzoate relative to hippurate suggested phase II liver biotransformation pathway (glycine conjugation) insufficiency. D-arabinitol is specific for Candida species; though not frankly elevated, its level may be considered high-normal by some clinicians. (Units: µg/mg creatinine).

		Results	Reference Limits
Eosinophil protein X (EPX)	H	19	≤ 7.0 µg/g
Calprotectin		46	≤ 50 µg/g
pH	L	5.4	6.1–7.9
Fungi		Positive for Candida parapsilosis, Rhodotorula, and Trichosporon with microscopy and culture	

Figure 2 Functional Stool Testing. EPX elevation indicated inflammation. Low pH indicated GI microbial imbalance and the fungi findings suggested GI fungal overgrowth.

		Results	Reference Limits
Indolyl-3-acrylolyglycine (IAG)	H	161.8 µg/mg cr	4.6–9.5
Deltorphin II	H	37.7 µg/mg cr	0.9–25.5
Dermorphin	H	32.4 µg/mg cr	2.0–15.5
Leucine Enkephalin	H	29.6 µg/mg cr	0.7–16.0

Figure 3 Urinary polypeptides. Elevations have been found in ASD. IAG has been proposed as a potential diagnostic biomarker for ASD.

	Results	Reference Limits
IgG anti-gliadin	H 91	normal 0–19 units
IgA tissue transglutaminase	< 2	normal 0–19 units
IgA anti-gliadin	< 2	normal 0–19 units

IgG (total) Reactive Foods (blood)			
Amaranth (+1)	Egg (+1)	Onion (+1)	Sage (+1)
Asparagus (+1)	Eggplant (+1)	Oregano (+1)	Sesame (+1)
Beef (+1)	Ginger (+1)	Peanut (+1)	Soybean (+1)
Cheese (+1)	Lamb (+1)	Pineapple (+1)	Sugar, cane (+1)
Cinnamon (+1)	Milk, cow's (+2)	Pumpkin (+1)	Wheat (+2)
Clove (+1)	Milk, goat's (+1)	Rice (+1)	Yeast, baker's (+1)
Cranberry (+1)	Nutmeg (+1)	Rye (+1)	Yeast, brewer's (+2)

Figure 4 Celiac panel and food-specific IgG antibodies. Elevated IgG antigliadin antibodies suggested gluten sensitivity, and possibly gluten enteropathy. The IgG food panel showed a mild reaction to 28 foods. Both the positive gliadin reaction and IgG panel results strongly suggested intestinal hyperpermeability. IgE food allergies test (not shown) was negative.

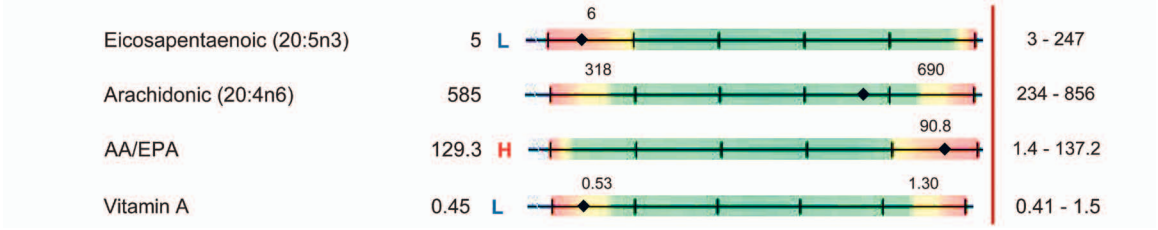

Figure 5 Plasma fatty acids and serum fat-soluble vitamins. Low EPA and normal AA. Taken together, these findings may be pro-inflammatory (the high AA/EPA ratio). Vitamin A level was low. Retinoid receptor imbalances have been linked to ASD pathogenesis and may be responsive to natural A supplementation.[21] (Fatty acid units: µM; vitamin A: mg/L).

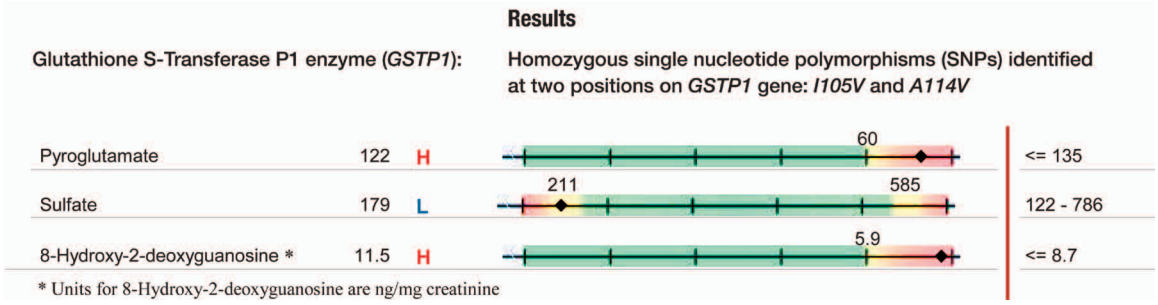

Figure 6 Markers relating to glutathione status and oxidative stress. GST enzymes are involved in phase II biotransformation; they are critical for biotransforming xenobiotic exposures, including both metallo- and organotoxins. GSTP1 is located in the brain and skin. Point mutations in GST enzymes have been found in ASD.[16,18] Urinary organic acids pyroglutamate and sulfate imbalance may demonstrate glutathione insufficiency. Elevated urinary 8-OHdG indicated significant oxidative stress. (Organic acid units: µg/mg creatinine, except as stated above.)

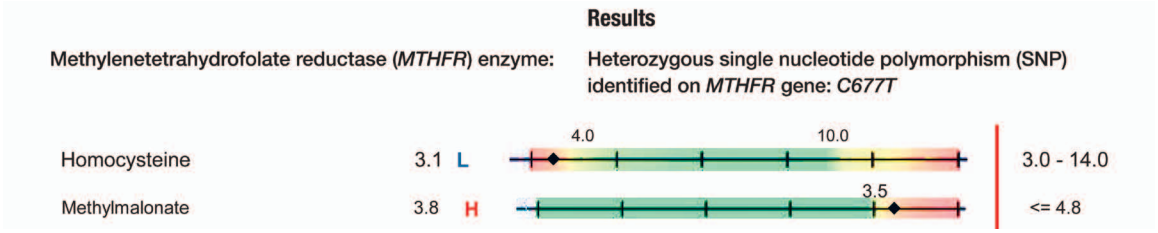

Figure 7 Methylation markers. The MTHFR heterozygous SNP may compromise methylation activity. Low serum homocysteine and a fifth quintile elevation of MMA (a functional marker indicating B_{12} deficiency) also may indicate compromised methylation activity. (MMA units: µg/mg creatinine; homocysteine: µmol/L).

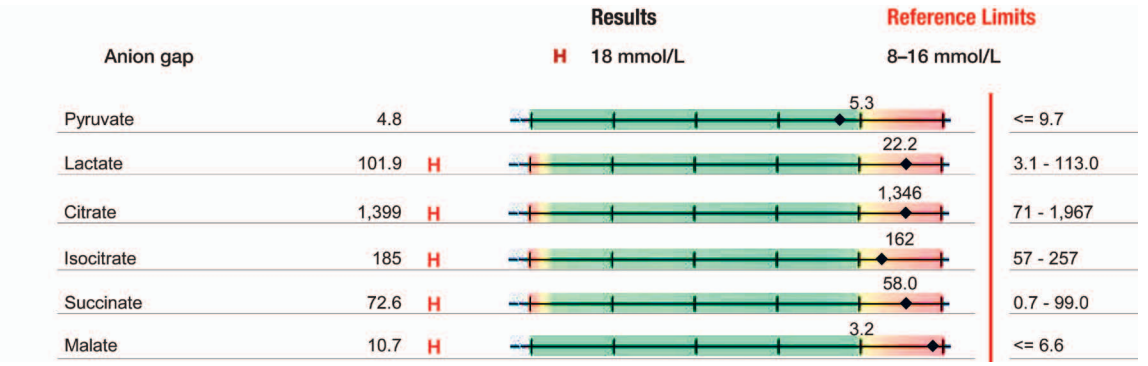

Figure 8 Urinary organic acids assessing mitochondrial function. The pattern of imbalance shown above (elevated citric acid intermediates) suggested a mild mitochondropathy requiring CoQ_{10} and a subclinical lactic acidosis. The elevated D-lactate in Figure 1 also contributed to lactic acidosis (units: µg/mg creatinine).

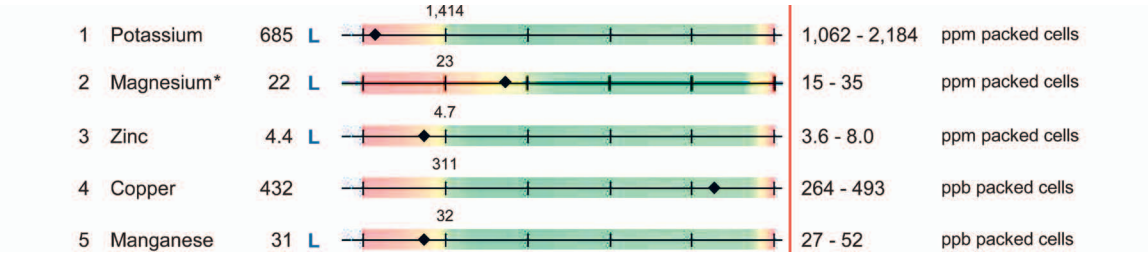

Figure 9 Erythrocyte essential elements. Levels were mostly low. The low quantity of zinc relative to copper has been seen in ASD.

- Comprehensive metabolic panel (CMP) and complete blood count (CBC) were within normal limits.

Initial Assessment

- PDD-NOS
- Irritable bowel syndrome with microbial dysbiosis
- Intestinal hyperpermeability
- Gluten sensitivity
- IgG food sensitivities
- Nutrient deficiencies
- Detoxification/biotransformation impairments:
  - Methylation
  - Hypohomocysteinemia
  - Glutathione conjugation
  - Glycine conjugation
  - Mild methylmalonic aciduria (B_{12} deficiency)
- Oxidative stress
- Mitochondropathy
- Mild lactic acidosis

Initial Plan

- Dietary Intervention
  - Diet: avoid all gluten-containing foods; continue to avoid dairy; minimize IgG food sensitivities x 3 months.
- GI Treatment
  - Rifaximin 200 mg, 1 tab PO TID x 7 days
  - Nystatin 500000 units, 2 caps PO BID x 3 months (after completion of antibiotic)
  - Charcoal capsules, 2 hours after medicine PRN
  - Probiotic combination 18 bill CF U, 1 packet PO QD
  - Digestive enzymes, 2 caps PO TID with meals
- Nutrient Support
  - Cod liver oil, 1 tsp PO BID
  - Multivitamin and mineral powder (specifically designed for ASD), 1 scoop PO QD
  - Zinc citrate 30 mg, 1 cap PO QD
  - Magnesium citrate 150 mg, 2 caps PO BID
  - Methylation support (folic acid, folinic acid, B_{12}, B_6, trimethylglycine, N-acetylcysteine, essential elements and nutrients), 1 cap PO QD

Treatment plan rationale: A variety of etiological factors (genetic and environmental) can contribute to the onset of ASD; laboratory assessment of children diagnosed with ASD often entails "casting a wide biochemical net" to capture the many possible imbalances contributing to the disorder.[11]

TL's food sensitivities required the elimination of gluten and a number of other foods. TL was also given Rifaximin, which is effective against small intestinal bacterial overgrowth.[22-24] Charcoal was offered as support if the bacterial die-off produced an increase in toxins and worsening of symptoms (Herxheimer reaction). Nystatin was used to eliminate TL's fungal overgrowth. Probiotics and digestive enzymes were initiated for the IBS, digestion and absorption.

Due to detection of the essential fatty acid, vitamin A and other nutrient deficiencies, cod liver oil (containing vitamin A) and a multivitamin mineral formula were started. Multivitamin and mineral formulas designed for children with ASD may be powdered, and frequently include higher doses of nutrients commonly found deficient, such as B vitamins

and zinc. Normalizing methylation and sulfuration (methylation) was also a key step for TL, as it is for most autistic children. B_{12}, folinic acid, and trimethylglycine have been shown to improve a number of metabolic activities, including glutathione synthesis. TL was also given higher amounts of magnesium and zinc, as he required more than his multivitamin and mineral supplied.

Two-month Follow-up

After starting treatment, TL began speaking with a limited vocabulary almost immediately, with regular attempts at new words. He began interacting with people and demonstrated increased eye contact. His mood improved and tantrums decreased. His energy was better. His bowel movements became larger and loose but less odiferous. His skin rashes had worsened. TL didn't tolerate the dietary changes well. His parents stated that he craved the restricted foods like an addict. He started eating Play-Doh, which contains gluten.

Two-month Follow-up Plan

Continue with protocol and add:

- Fluconazole (Diflucan) 100 mg, 1 tab PO QD x 30 days
- Saccharomyces boulardii 250 mg, 1 packet PO QD
- Amino acid formula, 1 cap PO BID (contains glutamine, glycine, methylsulfonylmethane, N-acetylcysteine, taurine, glutathione, ornithine, and calcium-D-glucarate)
- CoQ_{10} 100 mg, chew 1 tab BID

Treatment plan rationale: Because TL continued to present with signs and symptoms of fungal overgrowth, including behavioral episodes and rashes, fluconazole was initiated. *Saccharomyces boulardii* was also introduced, as it has been shown to reduce GI inflammation, normalize stool consistency, and (in animals) reduce fungal overgrowth.[25,26] An amino acid formula was introduced to improve toxicant mobilization. CoQ_{10} was given to stimulate metabolism and support mitochondrial activity (mitochondropathy was suspected because of the abnormal citric acid cycle intermediates and L-lactate elevation seen on organic acids).

Laboratory Tests Ordered

- Urine toxic elements (with oral DMPS provoking agent)
- Organic acids
- Stool test

Four-month Follow-up

TL experienced remarkable and immediate improvement in bowel movement consistency with the introduction of *Saccharomyces boulardii*. Potty training had been initiated. There was an increase in self-stimulatory behaviors, such as turning lights on and off and wheeling back and forth, but in general he was doing well. He was a well-liked child, enjoyed school, and was in a good mood most of the time. Parents noted that if probiotics were missed, TL's bowel movements immediately became large and loose. Parents requested a simpler supplement protocol, as he was taking 19 items per day.

Four-month Follow-up Laboratory Results

(See Table 4 for baseline and follow-up laboratory comparison.)

		Results	Reference Limits
Mercury	H	14 µg/mg creatinine	≤ 5 µg/g creatinine

Figure 10 Six-hour urine toxic elements (with oral DMPS). Mercury was elevated.

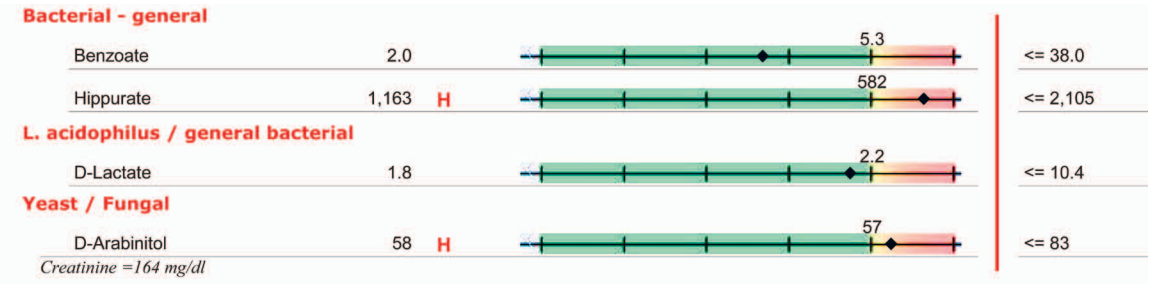

Figure 11 Urinary organic acids—compounds of bacterial or fungal origin. Improvement from baseline in all markers except D-arabinitol, which was elevated, indicating fungal overgrowth (units: µg/mg creatinine).

		Results	Reference Limits
Eosinophil protein X (EPX)		1.6 µg/g	≤ 7.0 µg/g
Calprotectin	H	90 µg/g	≤ 50 µg/g
pH		6.3	6.1–7.9
Fungi		Negative for Candida species, with microscopy and stool culture	

Figure 12 Functional Stool Testing. Results demonstrated improvement in EPX, pH, and fungi, but calprotectin was elevated, demonstrating continued inflammation.

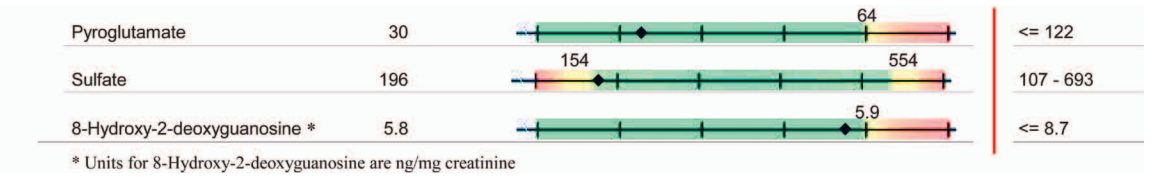

Figure 13 Urinary organic acid markers relating to glutathione status and oxidative stress. All markers were within normal limits (units µg/mg creatinine except as noted above).

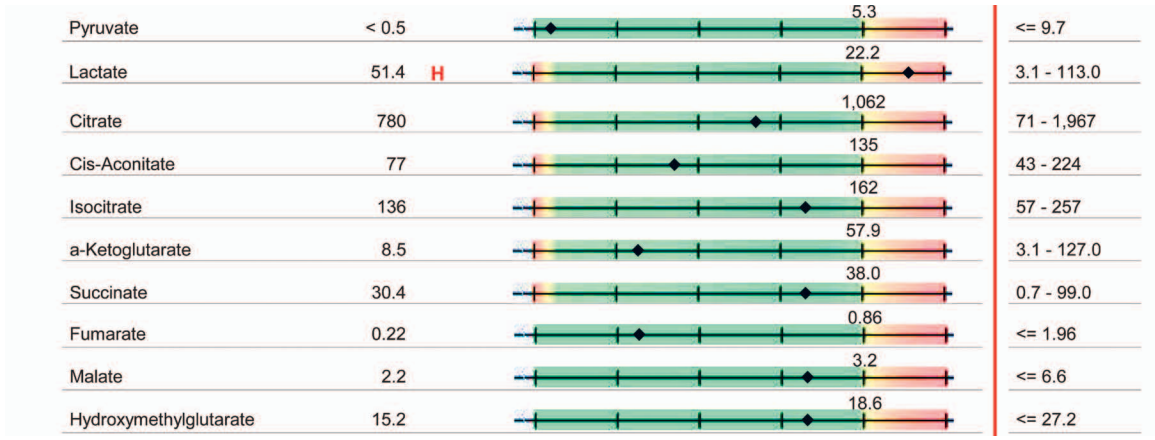

Figure 14 Urinary organic acids assessing mitochondrial function. All markers had significantly improved on follow-up assessment. L-lactate was still mildly elevated, but it was greatly improved from the initial L-lactate level (units: µg/mg creatinine).

Figure 15 Urinary organic acids—methylmalonate. MMA was higher than in previous testing, indicating a continued need for B_{12} despite supplementation (units: µg/mg creatinine).

Four-Month Follow-up Plan

- Discontinue the following:
  - Probiotic 18 bill CF U
  - Amino acid formula
  - Zinc citrate
  - Magnesium citrate
- Continue the following:
  - Digestive enzymes
  - Saccharomyces boulardii, 1 packet QD
  - Methylation support
  - Multivitamin and mineral powder
  - Charcoal capsules 2 hours after medicine PRN (to combat negative reaction to microbial toxins)
  - Continue gluten- and dairy-free diet
- Add the following:
  - Probiotic combination 450 bill CF U, 1 packet PO QD
  - Ketoconazole 200 mg, 1 tab PO QD x 14 days
  - Nystatin 500,000 Units, 1 cap PO BID x 3 months, to be started after completing the ketoconazole
  - Dimercaptosuccinic acid (DMSA) 100 mg, 1 tab PO BID between meals, every other week on M, W, F. Ensure regular bowel movements and sufficient fluids while taking DMSA.
  - Methylcobalamin pre-filled syringes 64.5 ²g/kg, SQ injection, three times a week
  - L-glutathione cream 1 gram, applied topically QD
  - Zinc sulfate cream 1 gram, applied topically QD
  - Magnesium sulfate cream 1 gram, applied topically QD

Treatment plan rationale: The 4-month follow-up plan was designed to address the continued yeast presence with 2 weeks of ketoconazole followed by 3 months of Nystatin, with concurrent aggressive probiotics. Per the parent's request, TL's protocol was simplified with the introduction of topical glutathione, zinc, and magnesium. Subcutaneous B_{12} was initiated, based on the continued elevation of methylmalonate.

Seven-month Follow-up Visit

The introduction of B_{12} injections caused a remarkable change in TL. He became more focused, able to spend 20 to 30 minutes on the same task at one time. He used more words and started to pronounce C, K, and G. He was generally less mentally "stuck." At first, the changes only occurred on the days he received the shots; his therapists often asked, "Is it a B_{12} day?" The changes eventually became constant. TL's therapists were reconsidering his diagnosis; whether he required a special needs school or could be mainstreamed. The plan was continued as directed.

Ten-month Follow-up Visit

TL began mainstream nursery school and was indistinguishable from the "normal" children. He loved school, did very well socially, and liked his routine. Without probiotics, his stools continued to be massive and loose. His parents had taken before and after videos. They were very pleased with his progress (Figure 16).

Up until two years of age, TL was developing at a normal level. His vocabulary was up to twenty words, but suddenly he started to regress. When we took him to see our pediatrician he was down to five words; three months later he couldn't say one.

After seeing a speech doctor and psychologists, he was diagnosed with pervasive development disorder or autism. We knew we had to do something because he wasn't getting any better. He was irritable and would throw tantrums all the time.

It wasn't until we discovered Dr Hyman that we started to put the pieces of the puzzle together. After going through Dr Hyman's program, we found that our son had several food allergies, heavy metal poisoning, severe gut inflammation, and imbalances in his gut bacteria as well as yeast overgrowth.

After learning about this we changed his diet right away and within days of removing dairy we saw immediate results. We saw more concentration. With the B_{12} supplements our son developed more verbal skills and was able to focus. What's amazing is that we didn't know there was a fog until we started eliminating the heavy metals (by chelation). After TL went through chelation he became much more alive, responsive, and verbal.

— TL's father

Figure 16 Father's comments. Description of TL's progress after 10 months of treating the underlying imbalances that were contributing to his ASD.

DISCUSSION

Onset of ASD is in childhood, frequently seen by 18 to 24 months and is characterized by abnormalities in social interactions, significantly impaired communication skills, and restricted repetitive and stereotyped behaviors.[27] Current estimates place the incidence of ASD at 1:91 to 1:110, with boys being affected four to five times more frequently than girls.[1] The etiology of ASD is multifactorial, with toxic exposures, pre-, peri- and postnatal infections, maternal infections, genetic abnormalities, nutrient deficiencies and vaccines being some of the implicated factors. Comorbidities include gastroenteropathies, allergies, autoimmunity and various psychiatric conditions.[7,9,16,20,28-30]

According to his parents, TL was a normally developing infant with a growing vocabulary. He was meeting developmental milestones, physically and intellectually. He had no family history that suggested he could be vulnerable to ASD. His parents noted that he experienced irritability after receiving all vaccines, which is not an uncommon occurrence. However, his parents also noted that there was a temporal correlation between his first MMR shot and the onset of PDD-NOS. MMR vaccine has been associated with the onset of ASD and ASD-associated gastroenteropathy, although there has been a great deal of controversy with this observation.[31,32] TL apparently experienced a significant in utero exposure to mercury and possibly, as an infant, to lead and insecticide. He was intolerant of dairy products and had symptoms consistent with allergies and irritable bowel syndrome.

Figure 1 demonstrated an elevation of D-lactate, accumulation of which can lead to systemic acidosis. Signs of acute toxicity include altered mental status, disorientation and irritability.[33] Other signs of acidosis include a low stool pH, an elevated anion gap and elevated L-lactate. The cause of TL's lactic acidosis may have been carbohydrate malabsorption from gluten intolerance or bacterial overgrowth.[34]

Elevated benzoate, a constituent of some fruits and preservatives, may be produced by intestinal bacteria.[35] Elevated benzoate but normal hippurate (Figure 1) pointed towards impaired conversion, suggesting a biotransformation pathway lesion.

D-arabinitol is specific for the presence of Candida species. While not frankly elevated, its presence may provide some corroboration for the finding of Candida species in the stool test (Figure 2).

TL's stool analysis results (Figure 2) strongly indicated inflammation. EPX is elevated in a number of GI inflammatory conditions, including gluten enteropathy and food allergies.[12] EPX is directly cytotoxic to the gastrointestinal mucosa,[36] contributing to intestinal permeability.[37] Calprotectin assay is sensitive for GI inflammation of organic origin but nonspecific for disease.[38] A low stool pH is associated with dysbiosis and acidic bacterial metabolites, including short chain fatty acids. Bacterial D-lactate producers thrive in an acidic environment. Alkalinizing the GI pH may therefore inhibit the growth of D- lactate, reducing systemic acidosis.[39] Multiple Candida species were also found, suggesting a lower-GI fungal overgrowth. Gastrointestinal candidiasis has been found in ASD and has been an alleged contributing factor in ASD symptomatology.

Elevation of the neuroactive dietary peptides (Figure 3) has been associated with ASD neurological and gastrointestinal symptomatology, and it is also indicative of intestinal permeability.[19] Elevation of IAG has been specifically associated with ASD and has been recommended for consideration as a diagnostic indicator.[40,41]

A marked elevation of antigliadin antibodies was shown in Figure 4. Antigliadin antibodies and gluten sensitivity have long been a concern with ASD patients, and gluten- free diets are often used with this population.[8,11,13-15] Research indicates that a gluten-free diet may reduce gastrointestinal inflammation in some ASD children.[42,43] The placebo arm of a double-blind placebo-controlled trial of a gluten-free casein-free diet for autism had to be discontinued due to the extent of improvement of the diet arm of the study.[44] Interestingly, while TL's IgG antigliadin antibodies (AGA) were markedly elevated, his IgA tissue transglutaminase and AGA were undetectable. Total IgA deficiency, a common finding among patients with celiac disease, has been observed in some ASD individuals.[32,45] In the presence of inadequate total IgA, the specific IgA antibody tests may have shown falsely negative results. Clinically, TL responded favorably to the removal of gluten-containing foods from his diet. ELISA testing for total IgG response to 90 different foods demonstrated a mild positive reaction (+1 and +2) to 28 foods, including wheat and dairy (Figure 2). The positive IgG wheat reaction is consistent with IgG antigliadin antibodies. Food sensitivities are closely associated with GI inflammation[46] and intestinal permeability.[47]

EPA deficiency is implicated in inflammation-driven conditions, including numerous neuropsychiatric disorders (Figure 5). Evidence supports the benefit of omega-3 supple- mentation in ASD children.[48,49] When EPA is in limited supply, enzyme and fatty acid substrate availability allows increased production of AA. Although TL's AA level was within normal limits, it exceeded the level of his EPA, resulting in an elevated AA/EPA ratio that can contribute to an inflammatory milieu.

TL had a very low vitamin A level (Figure 5). Autism may be linked to the disruption of the G-alpha protein, affecting retinoid receptors in the brain. Natural vitamin A may restore retinoid receptor function, which is involved in sensory perception, vision, language processing, and attention. The pertussis toxin found in the DPT vaccine may be involved in the G-alpha protein/retinoid receptor disruption.[21] TL's low vitamin A level may have been negatively affecting retinoid receptor activity, contributing to his autistic presentation.

TL had positive, homozygous SNPs in two different locations on the glutathione-S-transferase P1 enzyme (GSTP1) gene: I105V and A114V (Figure 6). It can therefore be concluded that both of TL's parents were at least heterozygous for the mutations. The GST family of enzymes catalyzes the conjugation of glutathione to various substrates for phase II biotransformation. SNPs in GSTP1 may significantly impair the ability to biotransform toxicants in brain and skin, where this enzyme is located. Classes of compounds biotransformed by this enzyme (glutathione conjugation) include toxic metals, xenobiotics, solvents, pesticides, herbicides and polycyclic aromatic hydrocarbons. Point mutations in the gene coding for glutathione s-transferase enzymes have been associated with increased risk of autism.[16,18]

Elevated 8-OHdG (Figure 6) indicated increased oxidative stress and identified the level of oxidative damage to the guanine residue of DNA. Guanine is the most easily oxidized of the DNA bases.[50] Given the GSTP1 SNPs, inflammation and poor methylation (or methylation lesion) and nutrient imbalances, the increased oxidative damage was not a surprising result.

TL was positive for a heterozygous SNP (C677T) in the gene coding for methylenetetrahydrofolate reductase (MTHFR). MTHFR is the enzyme involved in the final methylation step of folic acid, producing 5-methyltetrahydrofolate from 5,10-methylenetetrahydrofolate. Impairment of this enzyme is most commonly evidenced by an accumulation of homocysteine, since 5-methyltetrahydrofolate is required to recycle homocysteine back to methionine. However, abnormal MTHFR function has been noted in autistic children, who may also present with low to normal, rather than high, homocysteine levels, as found here (Figure 7).

James and Neubrander demonstrated in 2004 that treating ASD children with methyl donors including B_{12}, folic acid, and trimethylglycine normalized glutathione and homocysteine levels,[9,16] demonstrating the close relationship between methylation and sulfuration activity (Figure 17). Few laboratories consider low homocysteine to be alarming, despite its rate-limiting involvement in providing the cysteine residue for glutathione production. When oxidative stress increases, the enzymes involved in methylation are inhibited, thereby allowing homocysteine to be shunted into trans-sulfuration, producing glutathione. Homocysteine may be subject to depletion in chronic oxidative challenge, and low to low-normal levels are common in ASD children.

Furthermore, Deth et al suggested that the increased incidence of genetic polymorphisms found in methylation and sulfuration in ASD subjects significantly impacts methionine synthase (MS). Folate and cobalamin-dependent MS are involved in dopamine-stimulated phospholipid methylation. This signaling process, which is mediated by the D4 dopamine receptor, which promotes neuronal synchronization and attention, is also impaired in autism.[51]

Figure 7 also showed a fifth quintile elevation of methylmalonate (MMA). MMA is a sensitive functional marker of B_{12} (adenosylcobalamin) intracellular activity. Thus, methylmalonic aciduria is indicative of B_{12} insufficiency. Methylation and sulfuration pathway lesions are a common finding in autistic children, and may be relieved with high-dose methyl-B_{12} intramuscular injections.[7,9] Specific elevation of urinary methylmalonate has been noted in children diagnosed with regressive ASD and gastrointestinal symptomatology post-MMR vaccinations.[32] B_{12} therapy is generally considered to be a cornerstone intervention in ASD children.

Substantial laboratory evidence in this case for

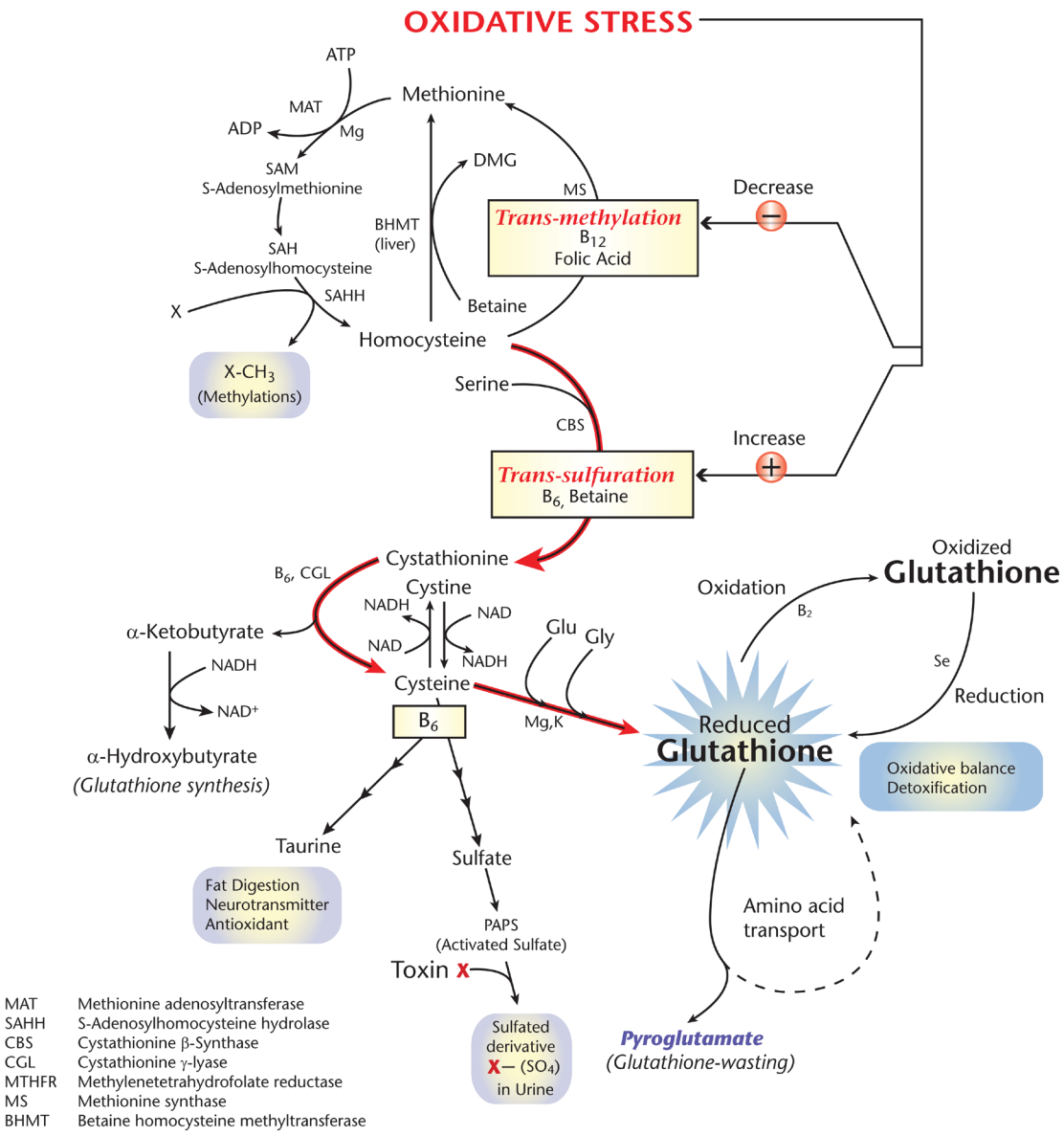

Figure 17 Methylation, sulfuration and oxidative stress. Under conditions of increased oxidative stress, enzymes involved in methylation are inhibited, allowing homocysteine to be trans-sulfurated to form glutathione. In ASD, there are documented genetic lesions in methylation and sulfuration, altering the normal physiologic response, resulting in lower glutathione and ineffectively controlled oxidative stress.

potential glutathione abnormalities included (a) elevated pyroglutamate (Figure 6), which may be indicative of limited glutathione availability via increased glutathione utilization or glycine insufficiency[52,53]; (b) low urinary sulfate, which indicated limited substrate availability for phase II sulfation and may also be correlated with low glutathione[54]; (c) the GSTP1 and MTHFR mutations, which can cause increased glutathione need, and decreased synthesis, respectively; (d) low homocysteine—a glutathione substrate; (e) B_{12} insufficiency also compromising glutathione synthesis; (f) low essential element cofactors, including B_6, potassium and magnesium—needed for glutathione synthesis; and (g) increased oxidative stress (8-OHdG) suggesting insufficient glutathione.

Elevations of citric acid cycle intermediates (Figure 8) and elevated L-lactate suggested mitochondropathy. There is a significant increased incidence of mitochondropathy in ASD children.[10,55] One study demonstrated mitochondrial dysfunction in ASD children with an elevated blood L-lactate/pyruvate ratio.[56] Phenotypic expression of the mitochondrial disorders, genetic and secondary, have been known to occur after exogenous toxic exposures, including vaccines, organo- and metallotoxins, and drugs.[55] Taken together, TL's elevated urinary D-lactate and L-lactate probably contributed to the slight elevation in the anion gap, causing low-grade metabolic acidosis.

A general pattern of low RBC elements suggested poor digestion and absorption. When essential ele-

Table 4 Select baseline and four-month follow-up laboratory result comparison. Improvements were noted in oxidative stress, lactic acidosis, mitochondrial function, and glutathione status. Gastrointestinal inflammation continued, and B_{12} deficiency had worsened. Improvements noted with (*).

Compound	Pre-test	Post-test	Reference Range	Percentage Change
Benzoate*	>160 H	2.0	≤38.0 µg/mg cr (fifth quintile < 5.3)	–99%
D-arabinitol	52	58	≤83 µg/mg cr (fifth quintile < 57)	+11.5%
D-lactate*	16.4 H	1.8	≤10.4 µg/mg cr (fifth quintile < 2.2)	–89%
Eosinophil Protein X*	19 H	1.6	≤7.0 µg/g	–92%
Calprotectin	46	90 H	≤50 µg/g	+96%
8-OHdG*	11.5 H	5.8	≤8.7 µg/mg cr (fifth quintile < 5.9)	–50%
Pyroglutamate*	122 HN	30	≤135 µg/mg cr (fifth quintile < 60)	–75%
Sulfate*	179 LN	196	122-786 µg/mg cr (fifth quintile 211-585)	+9.5%
Methylmalonate	3.8 HN	4.4 HN	≤4.8 µg/mg cr (fifth quintile < 3.5)	+15.8%
L-lactate*	101.9 HN	51.4 HN	3.1-113.0 µg/mg cr (fifth quintile < 22.2)	–50%

ments are in short supply, not only is metabolism compromised, but there may also be a risk of toxic metal uptake via essential element transporters in the GI tract and CNS.[57] TL's copper level was relatively high compared to his zinc. Low zinc availability will allow ready GI uptake of copper because they share transport proteins. Abnormal copper metabolism with low zinc and increased oxidative stress has been found in autistic children.[58] Zinc, copper, and manganese are all required for superoxide dismutase (SOD) in the mitochondria (Mn) and cytosol (Zn, Cu). SOD quenches superoxide radicals, and inadequate cofactors will compromise enzyme activity. Magnesium is required for more than 375 enzymes because of its presence in ATP. Magnesium (in ATP) is required to activate B_6 via pyridoxal kinase to pyridoxal-5-phosphate. Supplementation with both magnesium and B_6 has been shown to improve ASD symptoms and normalize RBC Mg levels.[59]

At his 2-month follow-up, TL was doing significantly better but continued to present with signs and symptoms of fungal overgrowth, including behavioral episodes and rashes, prompting the introduction of fluconazole. *Saccharomyces boulardii* was also introduced, as it has been shown to reduce GI inflammation, normalize stool consistency, and (in animals) reduce fungal overgrowth.[25,26] An amino acid formula was introduced to improve toxicant mobilization. CoQ_{10} was given to stimulate metabolism and support mitochondrial resuscitation (normalize citric acid cycle intermediates and reduce the L-lactate elevation).

At his 4-month follow-up, TL's urinary mercury levels were elevated (Figure 10), which was not unexpected given TL's in utero exposure to mercury via his mother's regular ingestion of tuna fish.

Figure 11 demonstrated a reduction in gastrointestinal microbial-produced organic acids. Particularly significant was the reduced benzoate and the improved conversion of benzoate to hippurate. The antimicrobials and dietary changes likely reduced the total benzoate load, while pantothenic acid (multivitamin and mineral) and glycine (amino formula) improved biotransformation to hippurate via glycine conjugation in the liver. The bacterial D-lactate producers were reduced, as reflected by the normal level of urinary D-lactate. This finding greatly eased concern about metabolic acidosis and encephalopathy, even though the L-lactate remained slightly elevated (Figure 14). Despite aggressive antifungal medication, the mild elevation of D-arabinitol (Figure 11) indicated the continued presence of *Candida albicans*.

Figure 12 demonstrated improvement in all stool markers, with the exception of calprotectin, which was now elevated. Calprotectin is derived from neutrophils and is a sensitive but not disease specific marker of inflammation throughout the gastrointestinal tract. In one study, fecal calprotectin was highest in children with organic bowel disease, vs controls and children with functional bowel disease.[38] Stool Candida culture was negative, despite the elevated D-arabinitol. It is possible that the Candida reservoir was extra-enteral, or in the upper bowel, and therefore not present in a stool specimen, which reflects lower bowel growth.

8-OHdG had previously been very elevated. As expected, with improved diet and nutrient intake, it normalized, indicating that oxidative stress had greatly declined (Figure 13). Pyroglutamate was well within normal limits and sulfate levels also normalized, indicating improved glutathione availability. L-lactate was still high-normal (Figure 14), although there was close to a 50% reduction. The citric acid cycle intermediates (not shown), L- lactate, 8-OHdG, and glutathione status had all improved, suggesting overall improved mitochondrial health. Oral B_{12} supplementation was not adequate to address TL's deficiency, as shown by the rising follow-up methylmalonate (Figure 15). Autistic children with GI lymphoid nodular hyperplasia, a condition associated with the MMR vaccination, had concurrent elevation of urinary methylmalonic acid.[32]

At TL's 10-month visit, he was reported as being in

mainstream nursery school, and was indistinguishable from the "normal" children. His parents took before and after videos. They were very pleased with TL's success, as TL's father notes in Figure 16.

CONCLUSION

ASD is currently the most commonly diagnosed pediatric neurodevelopmental condition. Since the 1980s, the incidence has increased an alarming 20-fold, from 5 in 10 000 to about 1 in 100 today with a higher rate in boys since the M:F ratio is about 4:1. Recent studies have suggested that there have been real increases and that at least 50% of the increases cannot be explained away by increased awareness, changed diagnostic criteria or diagnostic substitution (eg, children formerly labeled mentally retarded now diagnosed with ASD).[60,61]

Genetics and environment are both recognized as playing causal roles in ASD. Genetic lesions have been found in methylation, sulfuration, glutathione conjugation, the immune system, and the mitochondrial electron transport chain.[62,63] Genetic or epigenetic alteration to enzymatic function can increase cofactor nutrient demand.[64] Nutrient deficiencies due to poor diet or gastrointestinal malabsorption conditions, infections, food reactions, and toxic exposures are also potential triggers or disease mediators.[7,9,11,16,28]

An association between ASD and vaccines, including the MMR, has been suggested, although the validity of this claim has been challenged.[20,32] Indeed, a great deal of recent controversy surrounds the formal retraction of the 1998 Wakefield article that suggested a link between MMR and ASD.[31] At the same time, however, the argument for environmental impact on ASD precipitation (and many other diseases) is gaining support.[50,65-67] In this case, it appears that both toxic exposures and the MMR vaccine may have had roles in the development of ASD.

Although TL's recovery from ASD was dramatic, it is not considered rare among clinicians using a biomedical approach. Such an approach addresses the interplay of environment and genetics on central nervous system dysregulation, nutrient imbalances, oxidative stress, inflammation, and gastrointestinal pathology.[7,9,10] Because the metabolic lesions in ASD vary widely, laboratory evaluations are used to identify each individual's specific imbalances, allowing for individualized treatment.

Despite the successes, the greater medical community has struggled with fully recognizing the need for this whole-systems approach to treating ASD and often dismisses it by associating it only with extreme or risky practices without understanding the underlying principles or great range of low risk interventions. There is a need for more detailed case reports to be published in the peer-reviewed literature both to document efficacy and to detail practices to conventional medical practitioners who do not have training in the types of assessments and treatments that appear to be most medically effective for ASD. There is also a need to document the impact of functional medicine treatment regimens on neuropsychological and brain function. Such evidence would challenge the conventional framework that autism is purely a fixed genetically caused brain lesion.[68]

Given the surprisingly high and growing incidence of this disorder, well-designed trials are strongly needed to validate the efficacy of the biomedical approach to treating ASD. A functional medicine approach is well suited to designing a research methodology that, by honoring autism's daunting heterogeneity and complexity, has the best chance of succeeding in validating efficacy of this approach.

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