3 MEDICAL ISSUES IN AUTISM TREATMENTS

SEPARATING THE WHEAT FROM THE CHAFF

Contributed by Stephen Wellington, MD

From a parental perspective, one of the most overwhelming aspects of receiving a diagnosis of Autism Spectrum Disorder (ASD) for their child is the ocean of information available on the internet supporting biomedical interventions.

Many of these "treatments" rely heavily on testimonials and are exceedingly light on scientific data to support them! Many are very expensive, and while most may not do any physical harm to a child, a few can. Most importantly, they distract parents from focusing their resources on treatment that has been proven effective. This is not to say that parents should not engage in alternative treatments, but it is absolutely necessary to develop a critical attitude to the claims of those who make money from providing them.

To help parents and community professionals "separate the wheat from the chaff," ACT is grateful to Dr. Wellington for providing this review of medical topics related to autism, including the use of complementary alternative medicines. Stephen is a Developmental Pediatrician who specializes in children and youth with developmental disabilities, with a focus on the identification and management of children with ASD.

Stephen's background includes a Masters of Health Science in epidemiological and clinical research methods. He completed his PhD and post-doctoral fellowship investigating the molecular control mechanisms of developmentally regulated gene expression. His current research interests include involvement in a Canadian national study of the outcomes of children with autism in response to interventions. Stephen is also co-investigator on the Canadian-led international Autism Genome Project. He is a clinical assistant professor at the University of British Columbia, and is the Clinical Director of the British Columbia Autism Assessment Network (BCAAN).

Autism – The Role of Genetics

In general, disorders with a genetic component to their cause have a risk of recurring in subsequent children born to the original parents. In the absence of a specific genetic syndrome, the risk of the original parents having another child with autism spectrum disorder is currently estimated to be between 4% and 8%. In cases where a specific genetic syndrome has been identified, it is recommended that the family discuss recurrence risks with a qualified genetic counsellor.

For informed reviews on current research theories, see also the National Institute of Mental Health.[1]

To access genetic counselling or for a genetic evaluation for a child with ASD, ask for a referral to the Department of Medical Genetics, Children's & Women's Health Centre of BC. Email AspireBC@cw.bc.ca or call 604-875-2157.

MEDICAL TESTS

Is There a Medical Test for Autism?

At present, there is no specific medical test that is reliably predictive of a child developing autism or not. Although great advances are being achieved in the areas of genetic and brain research, one must exercise caution when reading popular media reports regarding new scientific discoveries regarding autism. As an example, let's consider when reports relate to the discovery of a new gene associated with autism.[2]

One must be aware of the limitations that are usually present with initial genetic findings:

- The genetic variant is often only present in a very small fraction (about 1%) of cases of children with autism that the researchers studied. In other words, about 99% of the other children had autism that was *not* associated with the variant in question. If one imagines that the test was performed on a hypothetical group of 100 newborn children destined to develop autism, only one of those children might be identified by the genetic test, and the other 99 would *still* grow up to develop autism (that is, the test would have provided false reassurance for those other 99 children).

- When the initial research studies analyze their volunteers who did *not* have autism, it is usually found that some of those volunteers had genetic changes to the *same region* of the chromosome. In other words, if the genetic test was performed on a hypothetical group of newborn children who were destined to *not* develop autism, the test would still indicate the presence of the genetic variant in some of those children (thus, the test would provide unnecessary anxiety for the family).
- In most cases, the genetic mutation associated with autism is newly formed in the child and does not exist in either parent. In other words, if parents wanted to be tested before they chose to have children, a negative test result would be no guarantee that their future children would not develop autism.
- Almost invariably, the function of the gene and/or how the genetic variant results in the development of autism has not yet been identified. In other words, for children already identified as having autism, finding the presence (or absence) of the genetic variant does not change what would be recommended for appropriate intervention.

The preceding discussion is not meant to diminish the significance of these types of research advances. Rather, it is meant to educate families that there is a necessary progression in biological research that is scientifically and ethically necessary before a newly discovered gene (or any other biological marker) can be considered an appropriate and/or reliable test for a condition as complicated as autism. Although this progression is ongoing, it still usually takes years from the time one first reads about the initial discovery before a given "test" is appropriately available outside of the research lab setting.

Why Did the Doctor Recommend This Test?

In general, in an otherwise healthy child, there is no "routine" set of tests that a physician will recommend just because a child has autism alone. Usually tests are indicated when there are *additional* features associated with a child's autism that might suggest:

- An alternative explanation *instead* of autism for the behavior and/or developmental pattern. For example, testing for hearing loss in a non-verbal 18-month-old child.
- A co-existing genetic, neurological, or metabolic condition that will have a significant impact on the management plan for the child or family. For example, if the behavior history or examination of the child suggests the presence of seizures, an EEG might be requested. Similarly, if the child with autism has an associated intellectual disability, genetic tests such as Fragile X and a high-resolution karyotype will likely be requested.

- The child is at increased risk for a health problem. For example, a child with autism who displays pica (the persistent eating of non-food items) is at increased risk to exposure to environmental toxins such as lead. Lead exposure is most reliably identified through a simple blood test. See also recent articles on children's toys found to contain lead paint.[3]

MEDICAL CARE OF CHILDREN WITH AUTISM

General Considerations

Like any other growing and developing child, children with ASD have basic health care needs, and benefit from health promotion and disease prevention activities, such as immunizations (see also below). However, children with ASD often have additional healthcare needs that can be related either to their underlying ASD (such as behavioral concerns) or the medical conditions that are commonly associated with ASD (e.g., certain genetic syndromes, epilepsy, pica).[4]

As a result, children with ASD often benefit from having involvement from a pediatrician familiar with autism who can evaluate and manage these additional medical considerations and/or help coordinate the various medical subspecialists involved in the child's care The physician's approach to the child must be considered in the context of their ASD, and ideally provides a "Medical Home" model of care[5] that is:

- Accessible.
- Continuous.
- Comprehensive.
- Family-centered.
- Coordinated.
- Compassionate.
- Culturally effective.

"My three sons with autism."

Donna Davidson

Points to consider for a physician delivering effective office care to a child with ASD include:

- Familiarizing the child with the office setting and staff.
- Allowing ample time while talking before touching the child.
- Allowing the child to manipulate instruments and materials.
- Keeping instructions simple.
- Using visual cues and supports.
- Slowing down the pace (often more time is required to complete an office visit compared to other children).
- Exaggerating social cues during interactions with the child.
- Including the family and/or familiar staff.

(See Resources: Scott M. Myers. Management of Children with Autism Spectrum Disorders.)

Special Considerations

It is beyond the scope of this chapter to review in depth all of the associated medical, health, and behavioral issues for children with ASD. However, a brief review of some of the more common medically related issues is listed below.

- **Diagnostic overshadowing:** Diagnostic overshadowing is the tendency for caregivers or clinicians to attribute new behaviors to the primary diagnosis (e.g., autism), when in fact they are due to a new condition. For example, in a child with autism who displays a sudden onset of "head-banging" behavior that is not responding to the typically successful behavioral interventions, one should consider that the head-banging behavior might be an expression of pain, rather than attribute it as part of the "autism." In this case, an underlying medical condition should be sought (e.g., is there an ear infection?).
- **Gastrointestinal problems:** Over a lifetime history, individuals with ASDs tend to have more frequent reporting (70%) of gastrointestinal symptoms (e.g., constipation, abnormal stool pattern, frequent vomiting) compared with children with other developmental disabilities (42%) or children without developmental disabilities (28%).[6] The current literature does not support routine specialized gastroenterological testing for children with ASD without symptoms indicating gastrointestinal problems.

- **Medications:** Medications are often used to treat behavioral problems, such as self-injurious behavior, hyperactivity, or anxiety, which keep the person with ASD from functioning more effectively at home or school. The medications used are those that have been developed to treat similar symptoms in other disorders.

  It is important that parents work with a doctor who has experience with children with autism. Although the doctor will prescribe the lowest dose possible to be effective, the child should be monitored closely while taking a medication. The American Academy of Child and Adolescent Psychiatry publishes helpful fact sheets which include questions that parents can ask their physicians about prescribed medications for behaviors.[7]

- **Nutrition:** Extreme food selectivity has the potential to lead to protein-calorie malnutrition or specific vitamin or mineral deficiencies; however, most studies that evaluated nutritional status in children with ASDs have suggested that despite dietary selectivity, malnutrition is uncommon in children/youth with ASD.[8]

- **Pica:** Pica is the eating of non-food substances. The definition of pica requires that the behavior be developmentally inappropriate and not part of a culturally sanctioned practice. Clay, dirt, ice, sand, feces, paint, and hairballs are just a few examples of what children and adults with pica have been known to eat. Children with persistent pica are at higher risk of exposure to environmental toxins (e.g., lead exposure) and should be tested for blood lead levels and indications of iron deficiency.

- **Puberty/sexual health:** Adolescence is a time of change, and it is no less so for teenagers with autism. Like all children, they need help in dealing with their developing sexuality and understanding their physical changes. For children with autism for whom sensory aversions are a significant behavioral challenge (as might occur with onset of menstrual cycles in females, or nocturnal emissions for males), families should consider planning behavioral strategies up to one year before changes are anticipated (in boys, pubertal changes start around age 10 to 14 years; in girls onset of menstrual cycles usually occurs between ages 10 and 16 years, or 2 to 2½ years after onset of breast development). In B.C., resources for helping address sexual health issues for children with disabilities are available through the Sunny Hill Education Resource Centre.[9]

- **Seizures/epilepsy:** Seizures, caused by abnormal electrical activity in the brain, can produce clinical symptoms such as a temporary loss of consciousness, a body convulsion, unusual movements, or staring spells. Although seizures are more common among children/youth with ASD compared to the general population, it is not considered common

enough to warrant automatic EEG testing of all children with ASD, without there first being clinical symptoms of seizure activity. In children with ASD with no other significant risk factors (e.g., severe intellectual disability, motor deficit, family history of epilepsy), the overall frequency of seizures is 6% to 8%. In general, the frequency of onset of epilepsy in ASDs has two peaks: one peak occurs before 5 years of age and the other in adolescence.[10]

- **Sleep disturbances:** Sleep problems are common in children and youth with ASDs. In some cases, there may be an identifiable medical cause, such as obstructive sleep apnea or gastroesophageal reflux. When there is not an identifiable medical cause, behavioral interventions are often effective, and there's some evidence that melatonin may be effective for improving sleep onset in children with ASDs (as well as children with other developmental disabilities).[10]

- **Vaccines:** In North America, routine childhood immunizations offer protection against viral/bacterial illnesses that can cause disease or death in young children. These diseases still exist, and outbreaks, even in developed countries, still occur. It has been estimated by the World Health Organization that if vaccinations were stopped, each year, 2.7 million measles deaths worldwide could be expected.[11]

  Some theories connect ASD with specific environmental factors or other triggers such as vaccines, and this has led to some concerned parents delaying or refusing routine vaccinations for their children. However, several well-designed international research studies have failed to show any links between the development of autism and receiving the mumps-measles-rubella (MMR) vaccine or the use of mercury-containing thimerosal preservatives in vaccines.[12] Furthermore, since 1994, none of the routine childhood vaccines administered in Canada have contained thimerosal.[13] Similarly, since December 2001 in B.C., the Hepatitis B vaccine has also been free of thimerosal.[14] Collectively, the information to date would strongly favour continued advocacy for all children to receive their routine childhood immunizations.[15]

ALTERNATIVE AUTISM TREATMENTS & TESTS

Complementary and Alternative Medicine

General Principles

The National Centre for Complementary and Alternative Medicine defines a complementary and alternative medicine (CAM) as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine."[16]

The use of CAMs is quite common in families who have children with ASDs. In one review, about one-third of the children with ASD had been given a biological (e.g., vitamins, chemicals) treatment that had no scientific proof that it worked. About 15% were using a biological treatment that had some evidence that it worked. Less than 10% were using a treatment that was potentially harmful. About 20% of the children had been given more than one therapy.[17]

Steps in Evaluating a CAM

Before investing the time, effort, and money to establish a CAM as a new intervention for a child with ASD, the family should consider the following.

1) Are the claims for the CAM bogus?

The Internet is full of information, but this is generally unregulated in terms of quality, and like any other consumer, the family reviewing a new intervention claim for autism needs to have a "buyer beware" attitude. As discussed by Dr. Barrett from Quackwatch:[18] "Quackery" derives from the word quacksalver (someone who boasts about his salves). Dictionaries define quack as "a pretender to medical skill; a charlatan."

Families should exercise caution when reviewing an intervention or product with the following claims or situations:

- Treatments that are based on overly simplified scientific theories.
- Therapies that are claimed to be effective for multiple different, unrelated conditions or symptoms.
- Requires you to suspend your belief system and adopt theirs (for example, asks you to "believe" in things that don't make common sense, or tells you that the treatment won't work unless you believe in it).
- Claims that children will respond dramatically and some will be cured.
- Promises to be effective for all children.
- Claims to improve all of the symptoms of autism.

- Claims to be the best treatment for your child or the only treatment your child needs.
- Treatments that are said to have no potential or reported adverse effects.
- Use of case reports, anecdotal data, or testimonials, rather than carefully designed studies to support claims for treatment.
- Lack of peer-reviewed references or denial of the need for controlled studies.

2) Is there evidence to support the CAM's benefits as an intervention for ASD?
Be an informed consumer. Find out what scientific studies have been done on the safety and effectiveness of the CAM treatment in which you are interested. To be accepted as a proven treatment, the CAM should undergo clinical trials, preferably randomized, double-blind trials, which would allow for a comparison between treatment and no treatment. Unfortunately, such studies are time consuming and expensive to perform properly, so very few CAMs have undergone this level of scrutiny. A recent review by Myers[19] of CAMs that had been evaluated by adequately designed studies indicated that the following treatment methods made no significant difference to the core features of autism:

- Auditory integration training.
- Dimethylglycine.
- Facilitated communication.
- Omega-3 fatty acids.
- Secretin.
- Vitamin B6 and magnesium.

3) Is the CAM potentially harmful?
Some of the CAMs could interact with prescribed medication, so it is important that parents let their child's doctor know what alternative therapies are being used.

With respect to chelation, "Unless there is clear evidence of current heavy metal toxicity, chelation by any method is not indicated outside of monitored clinical trials."[20] Chelation works for removing certain heavy metals like lead because they have two positive charges which bind tightly to the synthetic amino acid of the chelating agent (e.g., Na_2 EDTA). The problem is that other positively charged elements that are essential for cellular function (e.g., calcium and magnesium ions) can also bind to the chelating agent, and if not carefully monitored, drop to dangerously low levels. Intravenous chelation can be particularly risky, and at least one child with autism has died as a result of chelation with Na_2 EDTA.[21]

4) How do I evaluate the effectiveness of a CAM in my child (N of 1 studies)?
An "N of 1 study" is one in which the number of children in a study is only one. In the most scientifically reliable studies, the "N" can number in the thousands. However, careful observation of one child, yours, is important in deciding whether a CAM is worth continuing. When beginning a new intervention, it is important to be as objective as possible to determine whether the CAM truly improved the core features of autism and/or other targeted behaviors. If the treatment is not helping, then it does not make sense to continue, especially if it involves a great deal of time, money, or effort.

Some possible strategies to help determine whether the child may have improved from a specific treatment are reviewed below:

- Test only one CAM at a time. If a child improves after receiving several different types of treatments, then it is impossible to determine which one(s) were responsible.
- Use a checklist to help record the child's behaviors. Follow as many areas as you think are important or the CAM in question is supposed to benefit (e.g., eye contact, language/communication, joint attention, creative play, behaviors, sleep, etc). Rank the behaviors on a scale (e.g., 0 = no problem; 1 = mild problem; 2 = moderate; 3 = severe problem). Record the child's response to the CAM over at least three distinct phases:
    - Baseline: Prior to starting the intervention, record the baseline behaviors of the child on a daily basis for about two weeks.
    - Treatment: During the treatment phase with the CAM, record the behaviors of the child on a daily basis for about one month (actual duration depends on how fast the CAM is reported to start working).
    - Post-treatment: Stop the CAM, and continue to record the behaviors of the child on a daily basis for about one month.
- Additional records can be kept by a non-family member (such as a teacher). The additional observer should not be told when the CAM treatment starts or stops (this is called "blinding," since the individual can't see what CAM the child took at home or when the treatment started).

Note: Some background improvement is likely to be observed over the course of the three phases just by virtue of the child's natural development and/or continuation of standard therapy (e.g., ABA therapy). If there is additional benefit that can be attributed to the CAM alone, this should show up as significant improvement to the child's profile in the second phase, in com-

parison to phase 1 or 3 (this assumes there is no significant carryover effect of the CAM into phase 3 once its use has been stopped).

Some families go even further than what is described above, and work in collaboration with their physician's office or pharmacy to perform a randomized placebo-controlled blinded (n of 1) trial. (This is beyond the scope of this review).

Restrictive Diets and Vitamins/Minerals

Growing children need a balanced intake of calories, vitamins and minerals, and the nutritional needs of younger children are different than those of adults (e.g., higher fat requirements for children under two years). Children with autism often have behaviors and sensory issues that can make nutrient intake challenging.

Diets

CAMs for children with autism that are based on restrictive or elimination diets need to be approached with caution to ensure that the basic nutritional growth and development requirements of the child are still being met. In some studies, it has been noted that amino acid deficiencies are seen more often in children with autism on a restricted diet.[22] These potential risks need to be balanced against the general lack of well-designed randomized, blinded, placebo-controlled trials that would indicate that treatments such as the gluten/casein-free diets benefit the core social/communication symptoms of autism.[23]

Vitamins/Minerals

Different issues exist for vitamin and mineral supplement therapies. One consideration has to do with guarantees regarding the product quality and validity of advertising claims of the products sold in North America. In Canada, vitamin and mineral supplements are classified as "natural health products," which are regulated under the subset of "drugs" under the Canadian *Food and Drug Act*.[24] However in the United States, they are classified as "dietary supplements," which are regulated under the subset of "food" under the US Food and Drug Administration.[25] The consumer should note that this results in different sets of regulations governing the quality of these products in the two countries.

Another consideration is the potential for side effects. In some cases, large doses of vitamins (e.g., vitamin B6) and minerals (e.g., magnesium) can have undesirable or harmful side effects. For example, magnesium can cause diarrhoea at doses above 400 mg per day, and vitamin B6 can cause a sensory neuropathy or ataxia at regular doses over 200 mg per day.[26] Finally, there

are no appropriate blinded clinical trials that have shown that vitamin B6/magnesium combinations have any effect on the behaviors of children with autism.[27]

Diet/Vitamin/Mineral Trials

If the family is considering a dietary or vitamin supplement trial for behaviors in a child with ASD, it is recommended that they:

- Do so in conjunction with feedback from a nutritionist to ensure that a balance of nutrient intake is maintained.
- Choose a supply source of any supplement used (e.g., vitamin/mineral; other) that is safe and regulated.
- Inform the child's physician regarding the type and dosage of the supplements being considered, in addition to having the physician monitor the child's growth and development.
- Record the frequency of target behaviors, both before the trial commences, during the trial, and after the trial is stopped, in order that they can have some way to evaluate treatment response (see "N of 1 Studies").

Tests that Aren't Warranted or Are Not Meaningful

In general, a test is worth performing if three conditions are met:

1. The benefits of knowing the test results outweigh the risk of the test procedure. The term "risk" needs to be considered broadly. Within the public health care system, the physician is able to help guide the family regarding any potential health risks to the child that a test procedure might represent, and the test cost is borne by the public system. However, many families also seek testing for their children outside of the health care system. Although many of these other "tests" have arguably negligible health risks (e.g., sending a hair, urine, or stool sample for analysis), one also needs to consider the time, effort, and financial "risk" that these private testing procedures represent ($200 – $300 for a single private "fecal metal" or "urine neurotransmitter" kit), and note that the equivalent funding would pay for the cost of 2 – 3 hrs of 1:1 private speech language therapy.
2. The result of the test is going to change something we do for the child with autism in a significant and productive way.
3. We know that the test results are accurate and clinically meaningful. Not all tests are created equal. Some are a more accurate reflection of

what they are supposed to measure than others. For example, blood tests for heavy metals performed in a hospital reference lab are accurate, since they are collected and prepared in a standardized way that avoids contamination, and are compared to population-based norm-referenced standards. On the other hand, hair analysis for heavy metals is prone to many inaccuracies related to collection/preparation techniques, sample contamination, and lack of population-based norm-referenced standards.

Even when we are confident that a test result is "accurate," it does not guarantee that the result is clinically "meaningful." This is especially important in an evolving field like autism, where initial theories are put forward and might sound plausible, but are subsequently shown to be flawed or irrelevant to our diagnosis, understanding, or management of autism. A significant example of this was the link made between MMR vaccine, inflammatory bowel disease and autism, which was later discredited.[28] In these cases, even though there may be accurate tests available, it would be inappropriate to use them when the underlying theory relating the test result to autism is flawed.

With the above three considerations in mind, there is insufficient evidence to support the use of the following tests in the evaluation of autism alone:[29]

- Hair analysis for trace elements.
- Celiac antibodies.
- Allergy testing (particularly food allergies for gluten, casein, candida, and other molds).
- Immunologic or neurochemical abnormalities.
- Micronutrients such as vitamin levels.
- Intestinal permeability studies.
- Stool analysis.
- Urinary peptides.
- Mitochondrial disorders (including lactate and pyruvate).
- Thyroid function tests.
- Erythrocyte glutathione peroxidase studies.

Resources

- American Academy of Child and Adolescent Psychiatry: Facts for Families (www.aacap.org/page.ww?section=Facts+for+Families&name=Facts+for+Families).
- American Academy of Pediatrics National Centre of Medical Home Initiatives for Children with Special Needs: Autism Spectrum Disorders (www.medicalhomeinfo.org/health/autism.html).
- Centers for Disease Control and Prevention: Vaccine Safety (www.cdc.gov/ncbddd/autism/vaccines.htm).
- General reading resources on a variety of developmental concerns (including Autism) are available through the Family Resource Library at BC's Children's Hospital (www.bcchildrens.ca/KidsTeensFam/FamilyResourceLibrary/default.htm).
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- National Institute of Mental Health: Autism Spectrum Disorders (www.nimh.nih.gov/health/publications/autism/complete-publication.shtml#pub6).
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