



Research Brief

Virginia Tech Autism Clinic

Research Unit

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY

Our Purpose

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Around the world, specialty programs, clinics, universities, and government agencies are working to understand the causes of autism and to find solutions to the challenges that a child or adult with autism can face each day. Although in many cases scientists continue to have more questions than answers, important and useful information is steadily emerging from their work.

Understanding and keeping track of the latest research is a full time, and often overwhelming job, even for professionals who have dedicated their careers to doing so. Furthermore, autism research must address an extremely diverse array of factors, from communication to neurobiological mechanisms.

A wide range of possible causes and treatments are currently under investigation. Unfortunately, the lack of a consensus from the scientific community can be confusing for parents trying to best help their children. Several treatment options are available, but the scientific evidence

demonstrating their usefulness or lack thereof is not always readily accessible to parents.

This research brief is intended to provide parents, caregivers, and teachers in the New River Valley community with up to date information about ongoing treatment research relevant for children and adults with autism. Our hope is that this newsletter will serve as a practical and useful platform for sharing the information that researchers have uncovered.

This newsletter also will host information from the Virginia Tech Autism Clinic, Radford University Autism Center, and New River Valley Autism Action Group. The groups together form a coalition to address the needs of individuals with Autism Spectrum Disorder in the New River Valley of Virginia and surrounding areas.

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In future issues:

Results of Needs
Assessment for
People with ASD
in Virginia

Vitamin B6
& Magnesium
in the Treatment
of Autism

A Brief review of Casein and Gluten Free Diets as an Intervention for Autism

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Summary: *This is a brief review of the use of casein and gluten free diets as an intervention for autism and related disorders. Controlled studies using group designs were reviewed and evaluated using criteria for efficacy of treatments in clinical science. We conclude that there is currently little evidence for the efficacy of these diets in the general treatment of autism spectrum disorders. Guidelines for future research in this area are provided, and such studies are needed before firm conclusions of efficacy can be drawn.*

Only a handful of studies have evaluated gluten and casein free diets for children with autism.

The treatment of Autism, or Autism Spectrum Disorder (ASD), can be a complex and sometimes intimidating process for both parents and professionals. Dietary interventions, particularly casein-free and gluten-free diets, have become especially popular in the recent decade in treating autism. Although autism is considered a neurological disorder, some scientists suggest the disorder may have its origin within the digestive system; in other words, a genetic predisposition may be triggered by excess opioids from certain foods.

The reasoning behind the "opioid-excess theory" (see Panksepp, 1979) is that children with autism suffer from the inability to metabolize foods containing gluten (found in wheat and cereals) and casein (found in dairy foods), which in turn causes a buildup of peptides. Normally, peptides are broken down into smaller amino acids that cross the intestinal

membrane and enter the bloodstream; because peptides themselves are much larger they usually do not cross this membrane. Theoretically, children with autism will have an excess of peptides that their bodies cannot break down, and therefore more of these peptides may enter their bloodstream. Once in the bloodstream, these peptides act like opioids and can affect neurotransmitters in the brain, which could then cause changes in behavior.

In this way opioid over-activity, which can be detected in urine and cerebrospinal fluid, is suggested to cause problems that accompany autism, related to perception, cognition, and attention. Researchers point to studies reporting peptide abnormalities, an excess of peptides, in the urine of children with autism as supporting evidence (Cade et al., 2000). Based on this theory, researchers suggest that eliminating casein and/or gluten, which cause the buildup of peptides, from the diets of autistic children will eliminate, or at least greatly reduce, the severity of autistic behavior (Knivsberg et al, 1995; 2002; Whiteley et al., 1999).

A handful of studies have been conducted to evaluate the effect of these diets on children with autism, and these studies are reviewed here (Cade et al., 2000; Knivsberg et al., 1990; 1995; 2002; Reichelt et al., 1990; Whitely et al., 1999). It is

important to note that several studies in the literature report findings from the same sample (e.g., Knivsberg et al., 1990, 1991, 1994, 1995 which reported on the same sample of 15 subjects followed over 4 years; and Knivsberg et al., 2002, 2003 which reported on the same sample of 20 children using different measures). In these cases, we based our conclusions on the study which included the latest and most comprehensive information for the sample. For a case presentation refer to Adams and Conn (1997).

The following guidelines are standard criteria in clinical science used to evaluate an intervention. **First**, studies need to include a non-treatment (or other treatment known to be effective) control group to compare findings. This is very important because, without a control group, it is unclear if the children without treatment would have made the same changes for some other reason. **Second**, when there is a control group, there must be random assignment to the treatment group and the control group, meaning that each child has an equal chance of being in either group. This is needed in order to assure that each group is equal in all characteristics and not biased in any way. **Third**, when there is a control group, the raters or informers of outcome must be "blind" to group assignment, meaning they do not know which group the child was in. This ensures that the raters will not be inadvertently biased toward giving favorable responses to those in the treatment group. **Fourth**, in the absence of a control group, the research design must include repeated phases with and without treatment. This is rarely found in the research on casein or gluten free diets because of earlier case studies and anecdotal evidence suggesting that re-introduction of casein or

gluten can cause regression in some children. **Fifth**, the study findings must be replicated or repeated by an independent investigative team. This ensures that the findings can generalize or apply across study sites and is not a by-product of something unique to an individual research team. Furthermore, studies with large numbers of participants are considered to be stronger than those with small samples because findings from small samples are more easily influenced by idiosyncrasies of one or two individuals. It is also important that the sample of participants is clearly described, in order to know the characteristics of children who would be affected by the treatment.

These guidelines are provided to demonstrate that a research study of a specific treatment must meet basic requirements to be considered "up to standard" before we can claim that treatment to be effective or not. This review will place an emphasis on studies meeting the basic requirement of a control group (Knivsberg et al., 2002; Whiteley, et al. 1999), while also briefly acknowledging the others (Cade et al., 1999; Knivsberg et al., 1990; 1995; Reichelt et al., 1990).

Although the specific method varied from study to study, generally these studies have involved 1) removing all casein and/or gluten from the diet and then 2) evaluating the change or lack of change in autistic behaviors. It is important to note that in all of the studies children either had abnormal peptide levels compared to control samples, or were chosen to participate based on abnormal peptide patterns. As such, it is unclear how the findings

At this time, research in support of the use of gluten and casein free diets as a treatment for autism is relatively weak, and further research is necessary.

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apply to other ASD individuals with normal or unknown peptide levels.

Two studies and one follow-up study tailored the diet toward the individual needs of each participant (Knivsberg, 1990; 1995; Reichelt et al., 1990). The rest of the studies assigned the same diet regimen to all of the children. Most of the experimental periods lasted for one year, with the exception of one study that followed up after four years (Knivsberg et al., 1995) and another that only continued the study for five months (Whiteley et al., 1999). This latter study also did not randomly assign to groups. The research conducted so far suggests similar results. All of the studies that assessed peptide levels indicated a significant decrease in peptide levels in urine samples (Cade, 2000; Knivsberg et al., 1990; Reichelt et al., 1990; Whiteley et al., 1999), though the change was not necessarily correlated with the change in autistic characteristics.

The other studies did not report a follow-up urinalysis (Knivsberg et al., 1998; 2002). In the studies with a control group, some children showed increased skills while others' behavior worsened. Each study, however, claimed an overall improvement for children who participated in the gluten and/or casein free diet, reporting either a decrease in "autistic-like behaviors" (Knivsberg et al., 2002) or an increase in language and social skills (Knivsberg et al., 1990; Whiteley et al., 1999). Specifically, in one follow-up, four years after the study, increases in linguistic skills were noted (Knivsberg et al., 1995) although there was no comparison group alongside which to evaluate these improvements. Degree of improvement was determined from parent and teacher reports of "improvement" of symptoms

including attention, language, social skills and eye contact (Cade et al., 1999; Reichelt, et al., 1990).

Before drawing firm conclusions from this work, however, the studies must be considered in relation to the criteria discussed above. The majority of studies consisted of relatively small sample sizes ranging from 15 to 30 children. Only a minority of the studies we reviewed had a control group (i.e., children not on casein/gluten free diet) for comparison, and random assignment to groups (Knivsberg et al., 2002; Whiteley et al., 1999). To evaluate changes in autistic behavior, researchers in these studies initially collected data on the child's medical history and autistic symptoms. All of the studies accomplished this by using surveys or questionnaires in which parents were asked specific questions pertaining to their child's history. In some of the studies, non-verbal cognitive tests were conducted to measure cognitive abilities. Only one study used blind rating procedures, so that raters would not be influenced by knowledge of group assignment (Knivsberg et al., 2002). In all the other studies, the informants on the child's behavior knew which group the child was in.

In addition to the small sample sizes, the studies were conducted among a select portion of autistic children (those with peptide abnormalities) in a small geographic area, and each participant was chosen based on abnormal peptide levels. Each of these factors makes it less likely that the study findings will be meaningful for the general population of individuals with autism. Moreover, a diagnosis of autism does not necessarily guarantee abnormal peptide activity. Because autism is a

spectrum disorder, each patient diagnosed with autism expresses the symptoms differently and a significant proportion of children with autism do not appear to have peptide abnormalities. Furthermore, the casein/gluten free diets differed among the children in some of the studies. If each child was on a different diet, it is difficult to say which kind of diet is exerting an effect. It is also important to consider that compliance with diet was not monitored. Therefore, it is not certain that the diets were maintained as originally specified, or for how long or to what extent the diets were maintained. This information would be important, if not essential, for parents and practitioners to know in order to adequately implement the diet. With the exception of one study as noted above, changes in autistic behaviors were based on parent surveys and questionnaires rather than 'blind' informants. Parents have the advantage of being able to provide a complete report of their child's behavior. However, because parents knew their child was on a diet and would therefore be likely to expect improvements, they could very easily (even inadvertently) have been influenced by that knowledge when reporting improvements. Knivsberg et al. (2002) did include a few objective observational measures that would not be subject to parental bias, and did note improvements in these measures. This result is promising and needs to be replicated.

None of the research studies reported whether or not the children engaged in any other forms of treatment during the experimental trial, except for noting that a special educator phoned the parents periodically to discuss any concerns.

Behavioral therapy and specific forms of special education are very common among children with autism. If the children were involved in these other interventions as well as the diet, the improved behaviors cannot solely be attributed to the diet. Lastly, the improvements reported in these studies do not necessarily indicate improvements in the symptoms of autism as indicated by the Diagnostic and Statistical Manual of Mental Disorders – 4th Edition (1994), but rather, improvements in characteristics that are often associated with autism (such as disturbances in eating or sleeping, or sensory issues). The effects noted in most of the studies are small in magnitude. Further, as previously noted, these improvements are only seen in a subset of children with autism that display peptide abnormalities.

In conclusion, the evidence for casein/gluten free diets as an intervention for autism is intriguing, but not well supported in the research literature at this time. The studies we reviewed have shown improvements in some behavioral areas for children with autism, specifically those children with abnormal peptide levels. Moreover, only one of these studies met most criteria for a sound scientific design, including a control group, random assignment, blind raters, and objective measures (Knivsberg et al., 2002). Therefore, while these findings are encouraging, at this time the overall scientific evidence in support of casein/gluten free diet is weak. This conclusion is based on criteria used to evaluate the merit of treatment intervention research. As such, further research is critical

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to provide firm conclusions or clear evidence of efficacy.

In particular, future studies need to include 1) measures that are objective in nature or informers who are 'blind' to the group assignment, and therefore not potentially biased by expectations, 2) measures of actual autism symptoms in addition to associated characteristics, 3) larger sample sizes that are representative of the general autism population (i.e., not just children

with abnormal peptide patterns), 4) careful monitoring of diet compliance as well as other experimental period, and 5) replication by an independent investigatory team (i.e., other than treatments obtained over the Knivsberg-Reichelt team). Until such research is conducted, parents of children with ASD are urged to proceed carefully with such diets and only if their children manifest abnormal peptide activity.

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