Children and autism

Part 2 – management with complementary medicines and dietary interventions

BACKGROUND
Complementary and alternative medicines (CAMs) and dietary interventions are widely used in the management of autistic disorders as pharmacological treatments offered by mainstream medicine are limited and often associated with significant adverse effects.

OBJECTIVE
In this article, the rationale, safety and efficacy of a range of CAMs and dietary interventions used in the management of autistic disorders are discussed.

DISCUSSION
Despite many anecdotal reports supporting the efficacy of CAMs, evidence for their use in autistic disorders is either unclear or conflicting, and available data comes from a limited number of small studies. Large randomised controlled trials have not yet been conducted to examine efficacy in this population. Although most interventions are associated with only mild adverse effects, there is a lack of long term safety data. General practitioners need to be aware that the use of CAMs in autism is not risk free and often lacks sound clinical evidence. On the other hand, there may be subtle benefits to the child, especially if interventions are coupled with intensive behavioural and/or educational intervention.

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The use of complementary and alternative medicine (CAM) is increasing in the management of children with chronic illness or disability.[1–4] This is also evident in autistic disorder (AD) which has complex aetiology. A range of popular CAMs are also used in children with autistic spectrum disorder (ASD) with the intent to ameliorate the range of theorised biochemical abnormalities. Another reason commonly cited by caregivers for implementing CAM is that an autistic child's behaviour and sensory status frequently results in poor feeding behaviour and they have concerns about nutritional deficiencies.

Research reveals that an extensive range of CAM and dietary interventions are currently used in AD. A study by Levy et al[5] showed that more than 30% of children with autism were using CAMs and The Committee on Children with Disabilities reported up to 50% of children with AD in the United States are using some form of CAM.[6] Levy and Hyman[7] claim that out of 121 families studied, 56 and 61% had tried elimination diets and vitamin supplements respectively in their affected child. This is supported by Green et al[8] who conducted an internet survey and found that 27 and 43% of 552 parents with children with AD were using dietary interventions and vitamin supplements respectively. Witwer and Lecavalier[9] also examined treatment rates and patterns in 353 children with ASD and found that 15.5% were on a modified diet and 17.3% had taken some type of specially formulated vitamin or supplement. In addition, a semi-structured survey administered by the Quality Use of Medicines and Pharmacy Research Centre at the University of South Australia to 40 South Australian caregivers of children with AD to determine the usage of CAMs and dietary interventions, revealed that 35 (87%) of the families had tried or were currently using some form of CAM and/or dietary intervention.[10] Half of the families (50%) reported use of 2–10 different CAMs in their affected child(ren).

Evidence for the use of CAMs in autism

There is a lack of accurate, unbiased and evidence based information about CAM and dietary interventions available for parents and carers of children with AD. Ready access to information through the internet has contributed to the general increased use of CAM.[1] Families perceive CAM as a risk free approach that may improve their child's outcome.[1] All treatments used in children should be judged based on standards of scientific research. Studies supporting CAM

usage in AD need to be evaluated for scientific study design, clinical safety and scientific validity.[11]

Following is a summary of some CAMs used in autism that are currently popular and receiving attention. It is possible that a general practitioner will be asked by a parent or caregiver of the benefits and adverse effects of these CAMs.

Pyridoxine and magnesium

Nutritional supplementation with high dose pyridoxine and magnesium (HDPM) is claimed to have beneficial effects on the symptoms of AD and consequently it is one of the most popular CAMs for autism.[12] In humans, pyridoxine is involved in the synthesis of several neurotransmitters. Three randomised controlled trials (RCTs) have examined the effects of pyridoxine and magnesium in autism. A study by Kuriyama et al[13] comparing pyridoxine versus placebo found that verbal IQ improved in the treatment group while other studies by Findling et al[14] and Tolbert et al[15] found no significant differences in response between HDPM and placebo. The sample sizes of all studies were small (n=8, 10 and 15 respectively). While the side effects of HDPM appear to be mild in the short term, there is potential for significant side effects in the long term based on studies that have shown that high doses of pyridoxine cause peripheral neuropathy in adults.

Vitamin C

Vitamin C has a number of important functions in the body and participates in numerous metabolic pathways. It is a cofactor for neurotransmitter synthesis (conversion of tyrosine to dopamine and tryptophan to serotonin) and is well known for its involvement in antioxidant pathways and immune function regulation.[16] One small, double blind, crossover study (n=18) reported decreased stereotypic behaviours in children who received ascorbic acid.[17]

Dimethylglycine

Although there are numerous anecdotal reports that dimethylglycine (DMG) reduces autistic behaviours and improves speech, administration of low dose DMG demonstrated no statistically significant effect on autistic behaviours in two double blind, placebo controlled trials (n=8 and 37 respectively).[18,19]

Omega-3 and omega-6 fatty acids

Omega-3 and omega-6 fatty acids, recognised as vital building blocks for developing neurological systems, are also claimed to have beneficial effects in children with autism. These essential fatty acids (EFAs) are present in fish oils, evening primrose oil and linseed (flaxseed) oil.[20] One case report[21] and one comparative study (interrupted time series) without concurrent controls[22] have reported benefits of essential fatty acid use in autism. Gastrointestinal side effects are reported with EFAs including: nausea, diarrhoea, increased belching, acid/reflux/heartburn/indigestion, abdominal bloating, and abdominal pain. Fishy aftertaste is commonly experienced and rare reports of skin rash have occurred.[23]

Melatonin

Melatonin is another CAM currently receiving attention in the management of treatment of sleep problems in developmental disorders. Four RCTs have been performed that suggest melatonin may be effective at reducing sleep latency, or time taken for initiation of sleep, in children with severe sleep problems and developmental disabilities.[24,25] There is only one open trial conducted in a population of subjects with a homogenous diagnosis of an ASD.[26] Paavonen et al[26] found a statistically significant reduction in sleep latency with melatonin administration to 15 children with autism. Adverse effects of melatonin are generally reported to be mild and include: headache, dizziness, nausea and drowsiness, although an increase in seizure frequency in susceptible children is also reported. Overall, there is a need for clinical trials of melatonin to be conducted in a larger and more specific population before any firm conclusions about its use in children with autism can be made.

Probiotics

It is hypothesised that there is a link between ASD and gut dysfunction. Some children with autism experience loose stools and it has been reported that they have significantly greater levels of pathogenic organisms such *Clostridium histolyticum* in their faecal flora compared to typically developing children.[27] It has also reported that probiotics may produce benefits in this population, particularly if the child has received multiple courses of broad spectrum antibiotics and/or experiences enterocolitis.[28,29] Despite there being no published studies examining probiotic use in autism, they may be used to help restore the normal balance of gut flora and reduce the toxin producing bacteria that may be contributing toward gut dysfunction and exerting systemic effects with their metabolic products.

Vitamin B12

Adequate turnover of the vitamin B12 dependent methionine cycle is necessary to maintain normal methylation and antioxidant activity. James et al[30,31] conducted a study in which they administered intravenous methylcobalamin to eight children with autism who had been shown to have abnormal concentrations of methionine cycle metabolites. Supplementing the vitamin, in combination with folic acid and betaine, increased these metabolite levels to within the normal range and, most significantly, caused an increase in the ratios of oxidised-to-reduced glutathione to the extent that they no longer differed from those of the control children. This data suggests that vitamin B12 may aid in combating oxidative stress in children with autism. However, further research is required to confirm this effect and if there is any impact on the symptoms of autism.

Evidence for the use of dietary interventions

Elimination of casein and/or gluten from the diet of children with AD is a widely used intervention reported to improve behavioural symptoms.[28,32] It is theorised that impaired bowel permeability causes selective absorption of ingested peptides and exacerbates symptoms of AD.[33] To date, two RCTs have been undetaken to examine the efficacy of the gluten and casein free diets and conflicting results were obtained.[34,35] Knivsberg et al[34] found a statistically significant improvement in the dietary intervention group on multiple domains of autistic behaviours and traits, nonverbal cognition and motor skills when 20 children were studied. In contrast, Elder et al[35] found no difference between the groups on any

outcomes measured in a study of 15 children.

Other diets eliminating salicylates, food dyes, yeast and simple sugars have also been reported to have beneficial effects.[36] There is however no scientific evidence that establishes the efficacy of such diets in the treatment of autism in children.

If dietary interventions are implemented in autism, it is important to ensure that the child's restricted diet doesn't create nutritional deficiencies, and it is crucial that care is taken to assure proper nutrition.

Other controversial approaches to treatment

Overall, 22 publications of primary studies examining the use of secretin in children with autism have been conducted. It was concluded in a Cochrane systematic review of RCTs examining the use of intravenous secretin in ASD that there was no evidence of benefit.[37]

There are some studies that have indicated raised levels of heavy metals in the autism population.[38,39] There is a belief that autism is caused by a build up of heavy metals such as lead, mercury and arsenic in the body, as there are some similarities with heavy metal toxicity and autism.[40] It is also suggested that thiamine tetrahydrofurfuryl disulfide (TTFD) enhances the excretion of all four sulfhydryl reactive toxic metals: mercury, cadmium, arsenic and lead, and as such is used as a chelating agent in children with autism. To date, only one open design trial evaluating the use of TTFD in children with autism has been published and although it reported benefits in participants, there is not sufficient evidence to support its use.[39] Other forms of chelating therapy have not been scientifically studied and proven to be unequivocally effective or safe for use in AD.[41] Some forms of chelating therapy have been known to cause a range of significant side effects including hepatotoxicity and anaphylaxis.[42]

Metallothioneins are physiological proteins that naturally help to regulate the levels of redox active metals within the body. Redox active metals, such as copper and zinc, play an important role in the functioning of the nervous system but also contribute to the generation of toxic free radicals which can lead to tissue damage within the brain. In addition, these proteins form the first line of defence against toxic heavy metals as their structure incorporates multiple sulfhydryl groups.[43] Consequently, the theoretical use of 'metallothionein promoters' could be of benefit to autistic children, although there is a lack of solid evidence to support their use.

Glutathione is an important tripeptide with strong antioxidant properties and is a component of many bodily processes including DNA and protein synthesis, immune system functioning and enzyme activation.[44,45] The reductive ability of glutathione directly neutralises reactive free radical agents.[44] It is claimed that oral glutathione administration may help to reduce the impact of oxidative stress in children that is theorised to contribute to the aetiology of autism, however there are no studies to support its use in autism.

Evidence exists that autism may be associated with zinc deficiency in some children. Yorbik et al[46] found significantly lower levels of plasma and erythrocyte zinc in 45 autistic children compared to healthy controls. Zinc has a role in immune response, neurotransmitter production and has antioxidant properties, but despite the theoretical benefits of zinc supplementation in autism, there is still a lack of evidence for salutary effects in AD.

Conclusion

Because AD is a chronic condition for which there is presently no cure, it has become the focus of unconventional treatments. Often disenchanted by a health care system that appears to be able to do little to help their child, hopeful parents may turn to complementary and dietary therapies. It is important to discuss alternative therapies openly and compassionately. Although one needs to be cognisant of the emotional, time and financial impact of any intervention, if they are not causing harm to the child, there may be possible subtle benefits to the child, especially if the interventions are coupled with an intensive behavioural and/or educational intervention. However, large, RCTs have not been conducted to examine efficacy of many of these interventions.

Conflict of interest: none declared.

Acknowledgment

The assistance provided by Dr Barbara Anderson with the preparation of this article is acknowledged with gratitude.

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