CASE STUDY | Yeditepe Journal of Health Sciences, 13(1): 59-63

The Management of Autism by a Preventive and Pathophysiological Approach: A Case Report

Demet Erdoğan[1], Tijen Acarkan[1], Büşra Nizam[1], Burçin Tuvana Us[1], Ralf Herwig[2,3], Mehtap Kaçar[1,4]

[1] Department of Pathophysiology, Yeditepe University Institute of Health Sciences, İstanbul, Türkiye; [2] HG Pharma GmbH, Munich, Germany; [3] Heimerer College, Pristina, Kosovo; [4] Department of Physiology, Yeditepe University Faculty of Medicine, İstanbul, Türkiye

Abstract

The aim of this case report is the evaluation of the follow-up and treatment process in a patient with the diagnosis of autism spectrum disorder (ASD). A patient with ASD had social regression, limited eye contact, abdominal pain, and constipation. Urine lead, mercury and aluminum levels were above the normal range. Intestinal *flora* analysis found severe dysbiosis and intestinal inflammation. A combined preparation (*Chlorella vulgaris*, *Coriandrum sativum*, and probiotics) and a sugar, casein, and lactose-free diet were continued for one year. After 1 year; mercury level was normal and lead level was decreased. Constipation and pain were also relieved.

Keywords: Autism spectrum disorder, pathophysiology, heavy metals, phytotherapy, probiotics, diet

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition that is usually diagnosed in early childhood. The rapid increase witnessed in recent years compared to earlier dates has reinforced the hypothesis that environmental factors have a role in disease development. In several studies, exposure to environmental pollutants containing various toxic metals such as lead (Pb), mercury (Hg), aluminum (Al), and metallic arsenic (As) was blamed as an important risk factor in the etiology of ASD (1, 2). It was shown that exposure to toxic metals may cause neuroinflammation, particularly in the developing brain, and an increase in inflammatory cytokines. Within the neuronal cells, toxic metals may increase oxidative stress, may cause endoplasmic reticulum stress and essential metalloprotein degradation, and thus may lead to severe neuroinflammation, excitotoxicity and apoptosis (3). Observations in children with ASD have revealed

Received February 18, 2025 **Accepted** April 14, 2025 **Published** April 25, 2025 **DOI** 10.36519/yjhs.2025.633

Suggested Citation Erdoğan D, Acarkan T, Nizam B, Tuvana Us B, Herwig R, Kaçar M. The management of autism by a preventive and pathophysiological approach: A case report. Yeditepe JHS. 2025;1:59-63.

Correspondence Mehtap Kaçar **E-mail** mehtap.kacar@yeditepe.edu.tr

that there is at least one symptom associated with digestive systems in half of these patients (4). In recent years, scientists have suggested that intestinal dysbiosis may be one of the most important mechanisms in ASD pathophysiology. We have taken the etiologic mechanism of ASD and clinical signs of the patient into consideration, while planning the treatment of this patient.

CASE REPORT

Before the child was referred to us, a pediatric neurologist initially diagnosed him as being on the autism spectrum based on the criteria of Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV). According to the results of the Vineland Adaptive Behavior Scale (VABS), the child was behind his peers regarding communication skills and socialization areas and was referred to an ASD center for special education.

When he was referred to our clinic, he was two years old. In the first assessment he was socially regressed compared to his peers, he had repetitive behaviors and his eye contact was limited and he did not respond to verbal communication. Moreover, he frequently had recurring abdominal pain, constipation, and stool with a foul odor. The family was in search of preventive measures for his future life.

Toxic metal and intestinal microbiota analysis using the latest scientific information was planned for this patient to establish a firm diagnosis. Stool was collected for intestinal microbiota assessment and Stool Flora Scan (SFS) Plus® test (Laben Laboratories, Türkiye) was performed. The patient's flora index was measured as 13, indicating a severe imbalance in intestinal microbiota. According to the classification system used, scores between 8 and 14 reflect severe dysbiosis, while 0–3 is considered normal, 4–7 indicates moderate dysbiosis, and values above 14 represent very severe dysbiosis. Moreover, the calprotectin level — a biomarker of intestinal inflammation — was elevated 73 mg/kg (reference range: 0-50 mg/kg).

Table 1. Urine mercury, lead, and aluminum levels in 2009 and 2010.

	March 02, 2009	March 29, 2010	Reference Range (mcg/g)
Mercury	14.1	3	<5
Lead	25.9	19.5	<5
Aluminum	63	-	<60

The patient was sent to the Forensic Medicine Institute for toxic metal and mineral analysis. According to the institute's CDC-based protocol, urine was collected for eight hours after six tablets of DMSA 100 mg was given to the patient. The lead level in the urine was five times higher than the upper limit of normal (ULN) (25.9 µg/g), mercury level was three times higher than the ULN (14.1 µg/g), aluminum was a little higher than the ULN (63.2 µg/g).

We have planned to fulfill three treatment targets: detoxification by heavy metal chelation, regulation of intestinal flora and diet, and training the patient and his parents. For metal chelation, phytochelators (chlorella, coriander) were preferred. As phytochelators, a combination preparation containing both probiotic bacteria and *Chlorella vulgaris* and *Coriandrum sativum* was used as drop formulation. The treatment was started with one drop twice a day. With weekly increments, the dose was increased to daily twenty-six drops and the treatment continued for one year. After the treatment, from 2009 until the beginning of 2020 follow-up interviews were done for ten years, the frequency of interviews was two times yearly in the first three years and then annually. During this time, *Chlorella*, *C. sativum*, *Allium ursinum*, probiotics and prebiotics were used alternatively (5-7). To assist in microbiota regulation, a diet without refined sugar and carbohydrates was planned for the patient. There are several research showing the benefits of diet regulation for the treatment of children with ASD (8).

To keep the child away from toxic material the family preferred consumption of organic food, wearing organic clothing and using natural furniture without dye. The child's education was continued by instructions of a child development specialist between two to four years of age. By the inductively coupled plasma – mass spectrometry (ICP-MS) method, pre-treatment on March 2, 2009 and one year later post-treatment on March 29, 2010 values and reference range of heavy metals in the urine was listed, respectively. Mercury was normalized (from 14.1 mcg/g to 3 mcg/g; reference: <5), lead was decreased (from 25.9 mcg/g to 19.5 mcg/g; reference: <5) aluminum was slightly high in the first test, but there is no data about aluminum in the second test because of technical reasons. (Table 1).

After ten years, on July 19, 2019, toxic metal and mineral tests were repeated using ICP-MS/MS in blood samples in another laboratory. All the measured sixteen toxic heavy metal levels in the blood sample of the patient were found to be normal according to the laboratory's reference ranges (Table 2). SFS Plus® test could not be repeated due to financial reasons thus, flora index and calprotectin levels cannot be measured. However, clinical observations including stooling with foul odor, de-

creased constipation attack, and absence of abdominal pain showed that intestinal flora imbalance changed positively. There is accumulating evidence about correlation between ASD and environmental factors and gastrointestinal system (GIS) disorders. The best therapeutic approach seems to be early started preventive strategies.

Exposure to lead in earlier times of infancy may lead to neurochemical alterations, growth retardation neurotoxicity, decreased cognitive development, and a decrease in attention and executive brain functions (3). Although the accepted serum lead level in children is lower than 10 µg/dL, some studies have shown that even lower levels can cause neurotoxic symptoms (9).

It was shown that mercury exposure may lead to damage in organelles such as endoplasmic reticulum. The main target in mercury toxicity is the central nervous system. Both metallic and organic mercury may easily pass the blood-brain barrier and placenta and thus may be observed in breast milk and may be transferred to the fetus (3).

It is shown that compared with children without ASD, heavy metals such as mercury and lead were found to be significantly higher in children with ASD (10). In a meta-analysis of 48 studies, toxic metal levels of children with ASD were measured in various samples such as whole blood, red blood cells, serum, plasma, urine, and hair. Specifically, mercury and lead were higher in peripheral blood and red blood cells, and the authors reported the role of environmental factors in the etiology of ASD (11). Exposure to aluminum may suppress cellular energy synthesis by affecting several glycolytic enzyme pathways and may lead to neurotoxicity (3).

In children diagnosed with ASD it is assumed that there is a disruption in toxic metal elimination rather than exposure to toxic elements. The most preferred therapeutic approaches are avoiding exposure to toxic metals, elimination by metal chelation, supplementation of vitamin-mineral deficiencies, regulation of diet and treatment with antioxidants and anti-inflammatory drugs (12).

Since the tests indicated higher levels of these heavy metals in the patient, we aimed to eliminate lead, mercury, and aluminum heavy metals from the body of our patient by chelation therapy. Elimination of metal toxicity to relieve neuroinflammation and to correct intestinal dysbiosis was the mainstay of our treatment.

The use of chemical chelators which are rather used in acute toxicities such as DMSA, EDTA is limited due to their adverse effects that impede compliance. (13). We

Table 2. Blood mercury, lead, and aluminum levels in 2019.

	July 19, 2019	Reference Range (µg/L)
Mercury	0.2	<0.2
Lead	17.1	<28
Aluminum	<10	<11.4

preferred phytotherapeutic preparations. It is known that extract of *C. vulgaris* has a potent chelating effect on heavy metals such as lead, mercury, arsenic, and cadmium (14,15). *Coriandrum sativum* can mobilize heavy metals particularly mercury and lead from the tissues (6, 5). *Allium ursinum* contains numerous sulfur compounds including valuable sulfhydryl groups oxidizing mercury, cadmium, and lead and increasing their water solubility (7). Thus, *Chlorella*, *Coriandrum*, and *Allium* preparations that were used in our patients were produced from cultured plants and given in standard doses as drops or capsules that are chemically pure. After the use of phytochelators, heavy metal levels in blood were within normal levels in our patient. We also did not experience any side effects after phytochelation therapy. Gut microbiota affects brain development and behaviors *via* neuroendocrine, neuro-immune, and autonomous nervous systems (4). Alimentary tract symptoms observed in ASD may stem from altered intestinal microbiota. In ASD, increasing intestinal permeability and easy leakage of bacterial metabolites from the intestinal barrier is associated with a "leaky gut" and affects neurodevelopmental mechanisms in early childhood (16). In children with ASD who have taken probiotics, significant improvements in behavioral symptoms have been observed. Their bowel habits and behavior improved significantly when treated with probiotics containing five specific probiotic strains. These five probiotic strains are *Lactobacillus acidophilus* and *casei*, *Bifidobacterium bifidum* and *longum*, and *Lactobacillus delbrueckii* (17).

In children with ASD, there are some observations indicating the role of gut microbiota in occurrence of ASD symptoms and their severity such as correlations between severity of ASD symptoms and GI symptoms, definitive profiles of gut microorganisms and metabolites and numerous neurologic disorders stemming from the association between gut and brain (4,18). Many researchers have suggested that the increase of *Candida* spp. in gut flora and particularly *Candida albicans* may decrease carbohydrate and mineral absorption and increase toxin levels and thus may contribute to autistic behaviors (19). Increased calprotectin level in stool is considered as a

biomarker for inflammation. Calprotectin is a calcium and zinc binding protein released by neutrophils. In case of an inflammation in the GIS neutrophils migrate to the area and release calprotectin and thus calprotectin level increases in the stool (20). The patient had high calprotectin levels when he first came to our clinic. Although calprotectin levels cannot be measured after treatment, due to clinical improvement in GIS symptoms, we can argue that intestinal inflammation was recovered.

Families of children with ASD often refer to complementary and alternative medicine (CAM) practices. CAM practices are primarily preferred for improving health, treating specific symptoms, avoiding the adverse effects of conventional medicine, or relieving the main symptoms of ASD. Prevalent CAM categories are natural products, special diets, mind, and body therapies including acupuncture and chiropractic manipulations and other biomedical treatments such as probiotics, vitamins. Conventional studies have shown that some CAM therapies are ineffective, and some require more studies (21).

Training the parents is also important. Parent training is carried out by professionals of the subject by using various methods including didactic, role play, discussions, video guidance and thus information and skills are transferred to patients/caregivers.

We had a multidisciplinary approach in this case. While the patient was getting special education, we used a treatment using CAM practices. We chose phytochelators for heavy metal chelation, also supported this treatment with probiotics, vitamin supplementation and special diets.

CONCLUSION

This patient is now 13 years old with the help of family support, special education and the therapies mentioned above, he can build social communication. His academic success continues with minimal support, and he became an individual continuing his life with achievements in painting and music.

As it is obviously seen, a holistic therapeutic approach may be beneficial in ASD. After treatment by functional therapies and diet regulation and having support from a very considered family, it seems that it is possible for autistic individuals to participate in social life and continue their academic success by eliminating accumulated neurotoxic metals in children with a tendency to toxicity, correcting gut microbiota dysbiosis and perpetuating lifelong preventive therapies. However, more studies are needed in this area to optimize the therapy and establish a standard.

Ethics Committee Approval :N.A.

Informed Consent: Written informed consent was obtained from the patient's legal guardian to participate in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.K., D.E.; Design – T.A., B.N., B.T.U.; Supervision – D.E., M.K., R.H.; Data Collection and/or Processing – T.A., B.N., B.T.U.; Analysis and/or Interpretation – T.A., B.N., B.T.U.; Literature Review – T.A., B.N., B.T.U.; Writer – D.E., M.K., R.H.; Critical Reviews – M.K., R.H.

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Scientific Presentation: This case report was presented as an oral presentation at the 1st International Autism Meeting (IAMA), Alexandroupolis, Greece, 2019.

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