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CASE REPORT

Sequential Orthomolecular Stabilization and Empiric Folinic Acid Therapy in Regressive Autism Spectrum Disorder with Subsequent Folate Receptor Antibody Confirmation: A Case Report

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ABSTRACT

Background: Regressive autism spectrum disorder (ASD) involves loss of previously acquired developmental milestones and may reflect layered metabolic, mitochondrial, immunologic, and gastrointestinal dysfunction. Folate receptor alpha (FRα) autoantibodies have been described in subsets of ASD and may impair central nervous system folate transport. Folinic acid (leucovorin) has demonstrated benefit in selected patients.

Case Report: A female child with typical early development experienced regression at 11 months. At the clinical presentation (weight 13 kg; Autism Treatment Evaluation Checklist; ATEC score 60), she exhibited expressive language loss, social withdrawal, repetitive behaviors, and gastrointestinal instability. A structured orthomolecular program was initiated including dietary modification, microbiome stabilization, antifungal therapy, mitochondrial support, and subcutaneous vitamin B12 (75 mcg/kg) injections. Partial recovery occurred. Due to persistent expressive language plateau, leucovorin was introduced empirically and titrated, resulting in marked developmental acceleration. Subsequent FRα antibody testing revealed elevated binding antibodies (1.363 optical density; OD), retrospectively supporting the clinical response.

Conclusion: This case supports a systems-based orthomolecular triage model in regressive ASD and illustrates that empiric folinic acid may be effective when introduced after foundational stabilization. Laboratory confirmation may support, but need not precede clinical intervention.

Keywords: Folate Receptor Alpha (FRα) Antibodies; Folinic Acid (Leucovorin); Mitochondrial Dysfunction; Orthomolecular Therapy; Regressive Autism Spectrum Disorder

INTRODUCTION

Autism spectrum disorder (ASD) is a biologically heterogeneous condition involving oxidative stress, mitochondrial dysfunction, immune dysregulation, altered methylation capacity, and gastrointestinal disturbance (James et al., 2004; Rossignol & Frye, 2012). Regressive ASD commonly emerges between 9 and 24 months, coinciding with intense synaptogenesis, immune calibration, microbiome maturation, and heightened mitochondrial demand (Rossignol & Frye, 2012).

Cerebral folate transport impairment associated with FRα autoantibodies has been reported in subsets of ASD (Ramaekers et al., 2007). Folinic acid has demonstrated benefit in selected populations (Frye et al., 2018). This report describes a child with regressive ASD treated with layered orthomolecular stabilization followed by empiric leucovorin therapy and subsequent FRα antibody confirmation.

CASE REPORT

A female child demonstrated typical development through 11 months of age, including reciprocal smiling, babbling, and age-appropriate motor milestones. At 11 months, regression occurred with loss of expressive language, reduced eye contact, irritability, repetitive behaviors, and alternating bowel patterns. Past medical history included maternal hyperemesis, formula feeding, gastroesophageal reflux disease, asthma, and multiple antibiotic exposures. At age 2, the patient's weight was 13 kg and her baseline ATEC score was 60.

Clinical Findings

Upon clinical presentation there was notable echolalia, hand flapping, limited spontaneous communication, and gastrointestinal instability with undigested food. Organic acid testing demonstrated elevated arabinose and increased succinic and citric acid intermediates, suggesting fungal overgrowth (Herman & Herman, 2022) and mitochondrial stress (West et al., 2014)

Timeline

- Typical development (0–11 months)
- Patient regression (11 months)
- Plateau with patient development yielded ATEC score of 60
- Foundational orthomolecular stabilization plan implemented along with subcutaneous vitamin B12 injections
- There was partial recovery but it plateaued
- Empiric use of leucovorin
- Notable developmental acceleration
- FRα antibody testing was positive

Therapeutic Intervention

PHASE 1 – FOUNDATIONAL STABILIZATION

Gluten-free, casein-free diet; probiotic and digestive enzymes; botanical hepatic support (milk thistle tincture) and chlorophyll; nystatin; multivitamin with therapeutic amounts of vitamin B6, methylfolate, magnesium, and vitamin C; Acetyl-L-carnitine, Coenzyme Q10, biotin; omega-3 essential fatty acids and cholecalciferol.

PHASE 2 – REDOX AND METHYLATION SUPPORT

Subcutaneous vitamin B12 injections at 75 mcg/kg (1000 mcg per dose at 13 kg). Improvements included increased eye contact and emergence of expressive language.

PHASE 3 – EMPIRIC FOLINIC ACID

Leucovorin initiated at 2.5 mg twice daily and titrated to 7.5 mg twice daily. Marked acceleration followed with sentence formation and enhanced social reciprocity.

PHASE 4 – FRA ANTIBODY CONFIRMATION

Binding antibody positive (1.363 OD); blocking antibody negative.

FOLLOW-UP AND OUTCOMES

The Post-B12 phase reflected recovery of lost skills. The post-leucovorin phase demonstrated developmental acceleration beyond the prior plateau. The parents reported substantial improvements in language, connection, and functional participation. The repeat ATEC score decreased from 60 to 33. No adverse effects were observed.

DISCUSSION

ASD is increasingly recognized as a condition characterized by systems-level dysregulation rather than isolated neurodevelopmental divergence (Rossignol & Frye, 2012; Frye, 2020). The present case illustrates how multiple biological domains (redox balance, mitochondrial function, gastrointestinal integrity, immune modulation, and folate transport) may interact sequentially in a child with regressive autism. Importantly, the case highlights not merely therapeutic responsiveness, but the importance of intervention sequencing.

Dietary Foundations in ASD

Dietary intervention formed a foundational component of stabilization. Subsets of children with ASD demonstrate altered intestinal permeability, immune dysregulation, and reduced microbial diversity, factors that may contribute to systemic inflammation and altered neurochemical signaling (Hsiao et al., 2013; Kang et al., 2017). Increased gut permeability may permit translocation of dietary antigens and pro-inflammatory mediators capable of influencing central nervous system excitatory-inhibitory balance (Hsiao et al., 2013).

In addition to antigenic load, dietary chemical exposures – including food additives and other bioactive compounds – have been hypothesized to contribute to excitatory signaling stress in vulnerable individuals (Piwowarczyk et al., 2018). While clinical evidence for gluten- and casein-restricted diets remains heterogeneous (Piwowarczyk et al., 2018), reduction of dietary antigen and chemical burden may plausibly modulate immune activation and downstream redox demand.

In this case, dietary stabilization preceded methylation and folate-directed interventions. Lowering inflammatory and excitatory burden may have reduced overall redox demand, enhancing responsiveness to subsequent mitochondrial and neurochemical support. This sequencing reflects a systems-based approach in which gastrointestinal and immune stabilization precede targeted neurochemical intervention.

Gastrointestinal-Immune Interface

Gastrointestinal dysfunction is common in ASD and may contribute to systemic immune activation (Hsiao et al., 2013; Kang et al., 2017). Dysbiosis can influence neurodevelopment through short-chain fatty acid modulation, tryptophan–kynurenine pathway shifts, cytokine-mediated neuroinflammation, and increased intestinal permeability (Hsiao et al., 2013). Elevated arabinose in this case suggested fungal overgrowth. Nystatin, botanical hepatic support (milk thistle), and chlorophyll were introduced to reduce microbial burden and inflammatory load. Reduction of peripheral immune activation may decrease central neuroinflammatory signaling (Hsiao et al., 2013). This is relevant because folate receptor expression can be influenced by inflammatory mediators (Ramaekers et al., 2007). Thus, microbiome stabilization may indirectly enhance folate transport dynamics.

Redox Instability and Methylation Dysfunction

Impaired methylation and glutathione redox imbalance have been consistently described in subsets of children with ASD (James et al., 2004). Reduced glutathione (GSH) levels and altered GSH to oxidized glutathione ratios suggest chronic oxidative stress and impaired detoxification capacity (James et al., 2004). Because glutathione is central to mitochondrial protection, immune modulation, and neurotransmitter metabolism, redox instability may represent an upstream vulnerability node (Rossignol & Frye, 2012).

Vitamin B12 functions as a cofactor for methionine synthase, linking the folate cycle to homocysteine remethylation and glutathione recycling (James et al., 2009). Subcutaneous methylcobalamin therapy has been shown to improve glutathione redox status and may correlate with behavioral gains (James et al., 2009).

In the present case, vitamin B12 administration was associated with recovery of previously lost developmental skills. This suggests restoration of impaired function rather than acquisition of new skills and implies that metabolic bottlenecks, rather than irreversible neurodegeneration, were present. Without redox stabilization, downstream interventions may have been less effective.

Mitochondrial Vulnerability

Mitochondrial dysfunction has been documented in a significant subset of individuals with ASD, including abnormalities in oxidative phosphorylation, electron transport chain activity, and Krebs cycle intermediates (Rossignol & Frye, 2012; Frye, 2020).

Elevated organic acid markers such as succinic acid may reflect mitochondrial inefficiency or compensatory metabolic stress (Frye, 2020). The developing brain is highly energy dependent; synaptic plasticity and dendritic arborization are adenosine triphosphate (ATP)-intensive processes (Rossignol & Frye, 2012). Mitochondrial inefficiency during a developmental window may amplify vulnerability to regression (Rossignol & Frye, 2012).

Carnitine, CoQ10, and B-vitamin cofactors support mitochondrial membrane stability and ATP production (Frye, 2020). In this case, mitochondrial support preceded leucovorin therapy, reinforcing the principle that adequate cellular energy production may be prerequisite to effective folate-dependent neurotransmitter synthesis.

Folate Receptor Alpha Dysfunction

Cerebral folate deficiency associated with FRα autoantibodies represents a mechanistically plausible contributor to ASD in a subset of patients (Ramaekers et al., 2007). Binding and blocking antibodies may reduce folate transport efficiency at the choroid plexus, leading to relative central nervous system folate insufficiency despite normal serum folate (Ramaekers et al., 2007).

Folinic acid bypasses dihydrofolate reductase and may partially overcome receptor-mediated transport inefficiency. Randomized controlled trials have demonstrated improvements in verbal communication in children with ASD, particularly in those positive for FRα antibodies (Frye et al., 2018).

In this case, leucovorin was introduced empirically based on phenotype, i.e., persistent expressive plateau despite redox stabilization and positive response to methyl donor intervention (methylcobalamin and vitamin B6). Clinical acceleration followed, characterized by sentence formation, emotional reciprocity, and increased spontaneous communication.

FRα antibody testing was performed after clinical response and demonstrated positive binding antibodies (1.363 OD). Laboratory confirmation strengthened mechanistic plausibility, but was not required for clinical decision-making.

Recovery Versus Acceleration

A distinction in this case is the separation between recovery and acceleration. Vitamin B12 therapy corresponded with recovery of previously lost developmental skills. Leucovorin therapy corresponded with acceleration beyond the prior plateau.

Acceleration implies enhanced network integration rather than mere restoration and may reflect improved synaptic methylation dynamics, enhanced monoamine synthesis, stabilized redox environment permitting efficient folate utilization, and improved mitochondrial ATP supply enabling neuroplastic adaptation.

Sequencing as a Therapeutic Principle

Orthomolecular intervention may be most effective when structured hierarchically rather than applied as isolated nutrient escalation.

The observed therapeutic arc followed:

1. Terrain stabilization (diet, microbiome, liver support)
2. Redox and mitochondrial correction
3. Empiric targeted escalation (leucovorin)
4. Mechanistic confirmation (FRα antibodies)

While folinic acid may benefit subsets of patients, its magnitude of effect may depend on pre-existing metabolic stability.

Developmental Window and Neuroplasticity

The patient's regression occurred during a period of intense synaptogenesis and immune calibration. Early therapeutic intervention likely harnessed intact neuroplasticity to optimize recovery. The distinction between regression and recovery suggests that timely metabolic intervention during developmental vulnerability windows may alter trajectory.

LIMITATIONS

As a single case, findings cannot be generalized. Although post-treatment ATEC scoring demonstrated meaningful improvement (60 to 33), clinical outcomes remain observational and parent-informed. Controlled studies are required to determine reproducibility, optimal sequencing strategies, and predictive biomarkers of therapeutic response.

CONCLUSION

Sequential orthomolecular intervention followed by empiric leucovorin produced developmental acceleration in this child with regressive ASD. FRα antibody positivity provided mechanistic support, but was not required for initial decision-making. A systems-based orthomolecular sequencing approach may optimize clinical outcomes in biologically complex neurodevelopmental disorders.

ETHICS STATEMENT

This case report was prepared in accordance with the CARE Case Report Guidelines. Written informed consent was obtained from the patient for publication of this de-identified case report. All identifying information has been removed or altered to protect patient privacy.

CONFLICT OF INTEREST STATEMENT

The author declares no conflicts of interest related to this case report.

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AUTHOR CONTRIBUTIONS

Dr. Gannage conceived the clinical intervention, managed the case, and prepared the manuscript.

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