Case Series on Leucovorin (Folinic Acid) in Adolescents and Adults with Intellectual Disability

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Background

- Autism Spectrum Disorder (ASD) affects ~1 in 31 children in the U.S. Current FDA-approved treatments (risperidone, aripiprazole) target irritability rather than core symptoms.
- Cerebral Folate Deficiency (CFD) involves low CSF folate with normal serum levels, most commonly due to folate receptor alpha autoantibodies (FRAAs), which impair transport across the blood-brain barrier. FRAAs are reported in >75% of children with ASD in some cohorts.
- Leucovorin (folinic acid) bypasses impaired folate transport, increasing central folate levels. Pediatric studies suggest improvements in communication, behavior, and daily functioning.
- There have been limited studies in adolescents and adults.

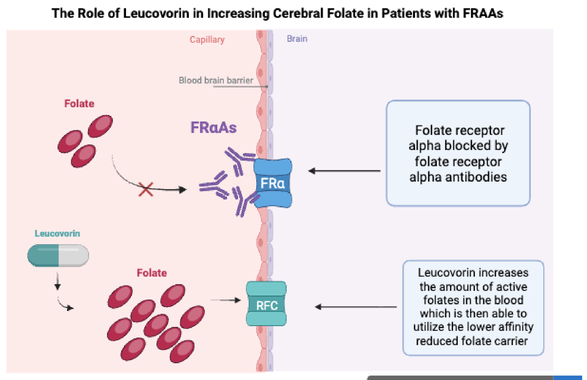

Figure 1. Illustrates one etiology of cerebral folate deficiency through folate receptor alpha antibodies (FRAAs) blocking the high affinity folate receptor alpha (FRα). Leucovorin helps to restore cerebral folate levels by increasing active folate concentration in the form of 5-Methyltetrahydrofolate to utilize the lower affinity reduced folate carrier to transport across the blood brain barrier.

FDA Approval

In March 2026, the FDA approved leucovorin for CFD associated with FOLR1 variants in pediatric and adult populations, based on existing literature. Prior studies show the largest effects on communication and moderate-to-large improvements in core ASD symptoms.

Response to Leucovorin in Participants With and Without ASD

Symptom	With ASD	Without ASD
Autism	67%	-
Irritability	58%	47%
Ataxia	88%	72%
Pyramidal signs	76%	33%
Movement Disorder	47%	18%
Epilepsy	75%	54%

Figure 2. Results from a meta-analysis for the prevalence of response to treatment with Leucovorin for participants with and without ASD. The percentages are the percentage of participants who showed improvement of the listed symptom with treatment of leucovorin. (Adapted from Rossigonl and Frye, 2021.)

Objective

To evaluate the use of leucovorin in adolescents and adults with ASD, particularly those refractory to standard treatments, including use without confirmed CFD.

Methods

Retrospective chart review of patients (ages 14–65 years old) treated with leucovorin via the Telepsychiatry Project of Ohio (December 2025–May 2026). Two patients identified. Outcomes assessed qualitatively via caregiver report of communication and behavior.

Case Presentations

Case 1:

27-year-old male with ASD, ID, ADHD, OCD, epilepsy, and tics. Severe aggression and limited verbal communication at baseline.

- Initiated on leucovorin 50 mg daily
- Early transient mood elevation
- Mild improvement in communication at 6–7 weeks
- Ongoing behavioral challenges; interpretation limited by psychosocial stressors and concurrent treatments

Case 2:

27-year-old male with ASD, severe ID, OCD, and longstanding aggression

- Initiated on leucovorin 25 mg BID
- Well-tolerated
- Minimal clinical improvement to date

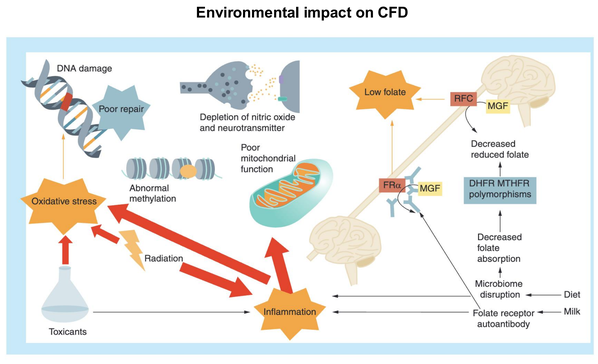

Figure 3. Effect of environmental factors on folate metabolism and its connection to reduced cerebral folate concentration. (Figure 4; Frye et al., 2017)

References

- Frye RE, Sequeira JM, Quadros E V., James SJ, Rossignol DA. Cerebral folate receptor autoantibodies in autism spectrum disorder. Mol Psychiatry. 2013;18(3):369-381. doi:10.1038/MP.2011.175
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- Rossignol DA, Frye RE. Cerebral folate deficiency, folate receptor alpha autoantibodies and leucovorin (Folinic acid) treatment in autism spectrum disorders: A systematic review and meta-analysis. J Pers Med. 2021;11(11). doi:10.3390/JPM11111141

Discussion & Conclusion

- Folate metabolism abnormalities are increasingly implicated in ASD. CFD is treatable, but diagnosis is limited by:
- Invasive testing (CSF 5-MTHF)
- Limited access to FRAA testing
- Incomplete sensitivity of genetic testing
- In this small adult cohort, leucovorin showed **limited but possible benefit** and was **well tolerated**. Interpretation is limited by confounders and small sample size.

Clinical Implications

- Leucovorin may be a **reasonable low-risk option** in treatment-refractory ASD
- Empiric use may be considered when CFD testing is not feasible
- Adult data remain limited

Limitations

This study is limited by its small sample size, retrospective design, and reliance on caregiver-reported outcomes. Lack of a control group, confounding factors, and absence of confirmed CFD diagnosis further limit interpretation and generalizability.

Conclusions

Leucovorin is a biologically plausible and well-tolerated intervention with emerging evidence in ASD. Larger studies are needed to define efficacy, optimal dosing, and predictors of response in adolescents and adults.

Diagnosis

- FRAA (FRAT) testing: limited access, not FDA-approved
- Genetic testing (FOLR1): recommended but incomplete
- Gold standard: CSF 5-MTHF (invasive, often impractical)

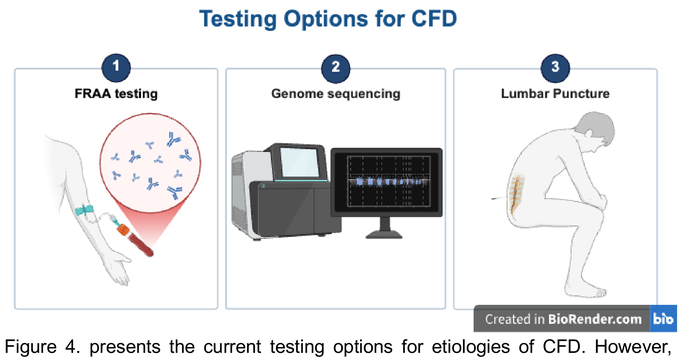

Figure 4. presents the current testing options for etiologies of CFD. However, Lumbar puncture is required for confirmation of reduced cerebral folate concentration.