

Does metformin slow cognitive decline in individuals with Fragile X Syndrome?

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Background

- Fragile X Syndrome (FXS) is one of the most common causes of intellectual disability. It is the result of the expansion of the trinucleotide CGG repeat (>200) in the fragile x messenger ribonucleoprotein 1 (*FMR1*) gene, leading to a deficiency or absence of the fragile X messenger ribonucleoprotein (*FMRP*)^{4,5}
- Many studies have found that there is a trend of IQ decline among FXS individuals around adolescent years^{2,7}
- Recent studies also found that metformin rescues some of the cognitive deficits in FXS mouse models, and case reports show similar benefits in FXS individuals^{3,6}
- This suggests that metformin may have clinical value as a targeted treatment to slow IQ decline in FXS individuals.
- In this follow-up study, we are assessing pre- and post-metformin IQ scores among individuals with FXS after > 1 year of treatment.

Objective

To observe the effects of metformin on changes in cognitive and adaptive functioning in a cohort of FXS individuals receiving metformin treatment.

Method

All participants were recruited from 3 sites: the MIND institute (n=8), Edmonton (n=13), STJ (n=3). Participants from all 3 sites were in a *Double-Blind, Placebo-Controlled Trial of Metformin in Individuals with Fragile X Syndrome* study and were recruited for a follow-up visit at least one year after starting metformin.

The baseline and follow-up visit consists of two assessments:

- **Cognitive assessment(primary outcome):** Leiter-III non-verbal IQ test
- **Behavioral assessment (secondary outcome):** Vineland III questionnaire

| Characteristics | Participants (N= 24) |
|--|---------------------------|
| Age (years) Range | 3 – 35 |
| Molecular marker | Full <i>FMR1</i> mutation |
| Duration on Metformin (years) Mean (SD) | 1.36 (0.50) |

Results

Table 1. Pre- and post- metformin non-verbal IQ scores and sub scores from the Leiter-III assessment

| | Pre-metformin | Post-metformin |
|--|---------------|----------------|
| Figure ground mean raw score (SD) | 15.04 (4.87) | 15.04 (4.34) |
| Form completion mean raw score (SD) | 19.12 (5.45) | 20.54 (4.38) |
| Classification & Analogy mean raw score (SD) | 13.25 (5.45) | 15 (6.22) |
| Sequential order mean raw score (SD) | 12.71 (5.87) | 15 (5.68) |
| Nonverbal IQ mean (SD) | 58.83 (15.08) | 58.4 (12.89) |

A paired sample t-test was conducted to compare non-verbal IQ score and subcategory raw scores on the Leiter-III pre- and post-metformin treatment. There was a significant difference between the raw scores for **form completion, classification & analogy, and sequential order (p = 0.025, p = 0.006, p = 0.015 respectively)**. There was no significant difference between the non-verbal IQ score and raw scores for figure ground (p = 0.750).

Table 2. Vineland adaptive behavioral scores pre- and post- metformin treatment

| | Pre-metformin | Post-metformin |
|---|---------------|----------------|
| Communication standard score mean(SD) | 48.6 (20.6) | 47.4 (22.3) |
| Daily living standard score mean(SD) | 69.5 (28.4) | 71.4 (27.8) |
| Socialization standard score mean (SD) | 64.6 (21.5) | 64.6 (24.4) |
| Adaptive behavior composite score mean (SD) | 59.9 (22.3) | 60.1 (23.6) |

A paired sample t-test was also conducted to compare adaptive behavior scores pre- and post-metformin treatment. There was no significant difference in adaptive behavior scores pre- and post- metformin treatment for the four categories of the Vineland: communication, daily living, socialization, and adaptive behavior (p = 0.97, p = 0.08, p = 0.63, p = 0.85 respectively)

Results Interpretation

- Due to the short duration on metformin (mean = 1.36 years), raw scores were compared as they can better show small changes in cognitive ability. Raw scores are also commonly used in clinical setting to assess cognitive abilities.
- Even though there is not a significant increase in IQ, it is important to note that IQ has remained stable for the duration of treatment. This finding is contrary to the typical decline among FXS individuals noted in the literature²
- There is a significant improvement in raw scores for classification & analogy and sequential order category (p = 0.006, p = 0.015 respectively), which require a higher level of cognitive ability compared to the first two sections of the Leiter-III: figure ground and form completion. This implies improvement in executive functioning among FXS individuals post-metformin treatment. There was no significant difference in figure ground raw scores, potentially because metformin does not work on visual processing
- In addition, the lack of decline in adaptive behavior, such as daily living and socialization is important to recognize as a similar decline to IQ is also noted for adaptive behavior in FXS individuals²

Conclusion

Even after a short duration of metformin treatment, we depicted a stabilization of IQ in our FXS participants instead of the decline around adolescent years previously noted in the literature. The next step in this study is to compare the cognitive ability and adaptive behavior in our participants to their age-matched FXS counterparts in the literature to see if there's an improvement in IQ scores. This will shed light on the efficacy of metformin as an additional therapy to slow cognitive decline in FXS individuals and improve their quality of life.

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