Spontaneous improvement of carbohydrate-deficient transferrin in PMM2-CDG

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Background & Objectives

- Phosphomannomutase 2 deficiency (PMM2-CDG) is the most common type of CDG (Congenital Disorders of Glycosylation) and presents with multisystemic organ involvement.
- Currently, there is no specific treatment. Several therapeutic options are in the pipeline, but it is impossible to perform well-powered, placebo-controlled, double blind studies for all of them in a timely manner.
- In this study, we used mass spectrometry based transferrin glycosylation results to investigate whether transferrin glycosylation, the typical diagnostic test, could serve as a reliable marker for future trials.
- We hypothesized that transferrin glycosylation shows spontaneous improvement in PMM2-CDG, since several CDG types show spontaneous improvement in glycosylated biomarkers, including transferrin.

Biochemical characteristics

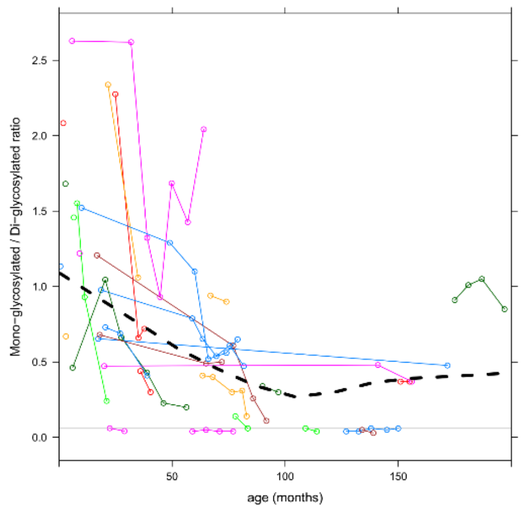


Fig 1: Measurements of transferrin glycosylation by MS (Mono-/Di)

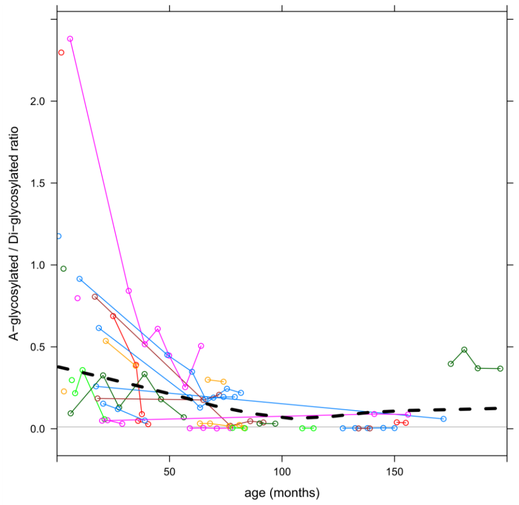
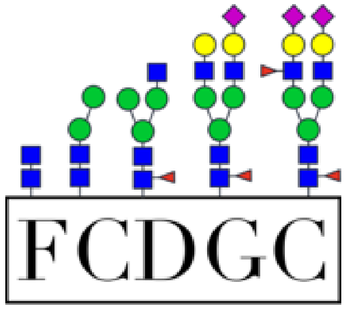


Fig 2: Measurements of transferrin glycosylation by MS (A-/Di)

Methods

- We performed a retrospective analysis of mass spectrometry based carbohydrate deficient transferrin (CDT) analysis results in untreated PMM2-CDG patients.
- These patients have been followed at our consortium sites in our ongoing prospective natural history study:
  - Mayo clinic (Rochester, Minnesota, USA)
  - Seattle Children's Hospital (Seattle, Washington, USA)
  - Children's Hospital of Philadelphia (Philadelphia, Pennsylvania, USA)



Results

- We collected 108 observations in 37 patients: 13 females, 24 males (age range 0.6 months-70 years); on average 3 measurements/patient (range 1-7 measurements)
- We found a clear, age-dependent improvement of transferrin glycosylation toward a more normal glycosylation pattern in patients with their first CDT analysis before the age of 100 months, as evident from the Loess regression (black dotted line):
  - decrease of mono-/di-glycosylated transferrin ratio from 0.76 ± 0.71 to 0.47 ± 0.45 ($P < 0.001$, Wilcoxon signed rank test, normal ratio value < 0.06)
  - decrease of a-/di-glycosylated transferrin ratio from 0.34 ± 0.51 to 0.18 ± 0.29 ($P = 0.031$, normal ratio value < 0.0111)
- Additionally, our data suggests a high variability in carbohydrate deficient transferrin results.

Conclusions

- This observation questions the reliability of transferrin as a therapeutic outcome measure in clinical trials for PMM2-CDG, given its trend toward spontaneous normalization with age.
- There is a need for clear clinical endpoints (e.g. improvement in Nijmegen CDG Severity score or Quality of Life Scores) or validated biomarkers to study upcoming therapies.
- It is critical to prepare clinical trials of new promising therapies with a carefully designed, prospective, multi-center natural history study to identify reliable biomarkers linked to clinical outcomes in CDG.

References

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