Beware of abnormal capillary electrophoretic pattern of serum transferrin: congenital disorder of glycosylation (CDG) type I can be associated with variant

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Background:

Type I CDG (CDG-I) is caused by defects in the biosynthesis of the lipid-linked oligosaccharide required for protein N-glycosylation in the endoplasmic reticulum. CDG-I screening is based on testing the glycosylation of serum glycoproteins such as transferrin (Trf). Abnormal glycosylation can be revealed by loss of electric charge, i.e. sialylation, or molecular mass changes, evidenced in our lab by Trf capillary electrophoresis (CE) or Western-blot (WB) of several glycoproteins, respectively.

Cases report:

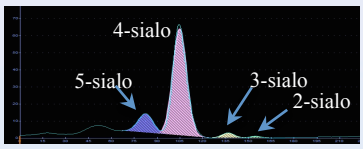
Among 1500 samples yearly screened using Trf CE in our lab, about 10 patients are diagnosed as CDG-I. Two of them were of special interest: Trf CE profiles suggested protein variant needing deeper investigations.

Case1: Lebanese newborn, mental retardation, cerebellar hypoplasia, molecular diagnosis in progress.

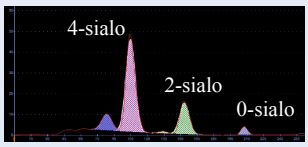
Case2: one-year old boy, epilepsy, cerebral atrophy, protein-loss enteropathy, abnormal coagulation. ALG8-CDG

Results:

Normal pattern:

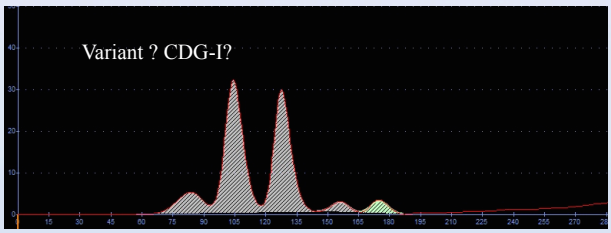


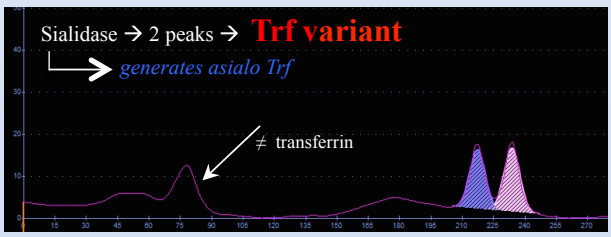
CDG type 1:



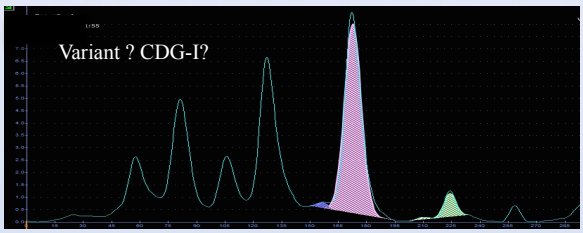
Capillarys 2 Sebia® CDT method

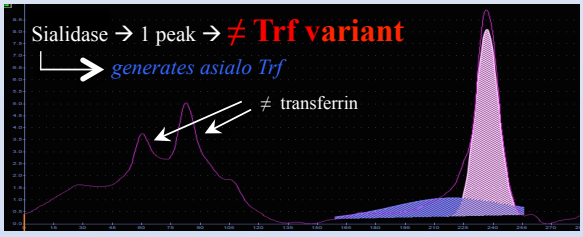
Case1



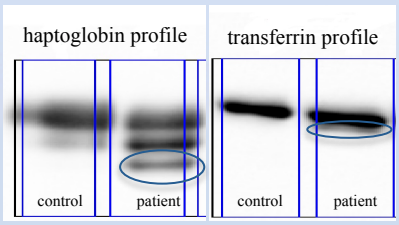


Case2



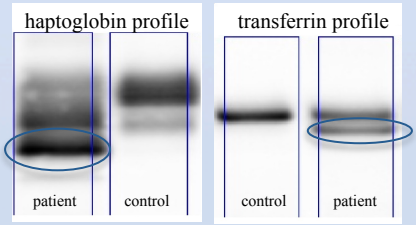


Serum treated by sialidase; phosphate buffer 50mM pH=6. Sialidase removes sialic acids and generates 1 peak in absence of variant (2 peaks if variant)



Additional bands on WB
→loss of entire glycan chains

→ Both cases are CDG-I



Conclusion:

Protein variants greatly complicate interpretation of transferrin CE profiles but can be easily asserted thanks to sialidase treatment. We showed here that in these difficult and relatively frequent cases, an additional screening technique such as Western-blot is highly recommended to definitively exclude CDG.