Hide and seek: a misleading transferrin variant in PMM2-CDG

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Case report

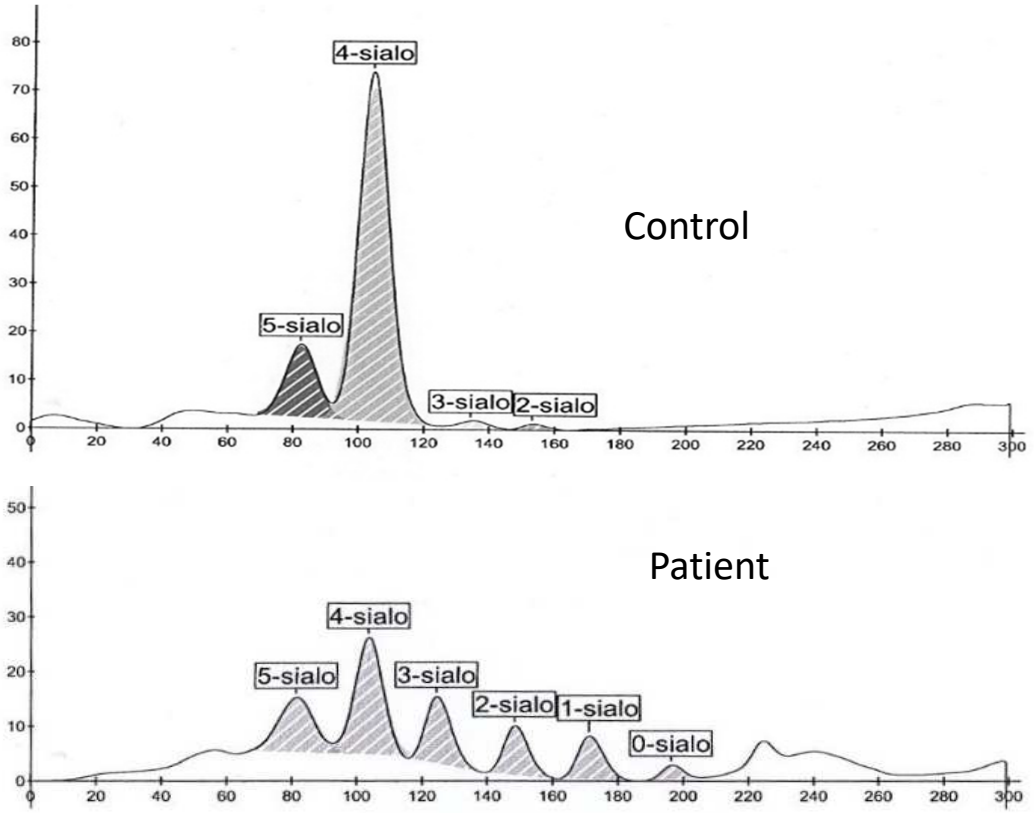
- Normal pregnancy, non-consanguineous Belgian parents.

- At 6 months, the patient was placed into foster care. Axial hypotonia, pressure ulcers, cryptorchidism, strabismus, intermittent nystagmus, and facial features reminiscent of fetal alcohol syndrome. Parental drug and alcohol abuse were suspected. At 1 y.o, brain MRI was normal.

- At 2 y.o, the patient was referred because of persistent global DD. Slight dysmorphic features: large, low-set ears, thin upper lip and a flat philtrum. Fingers were long and slender. No peculiar fat distribution, the nipples were widely spaced and flattened but not inverted. Mild axial hypotonia, joint hypermobility and strabismus. Failure to thrive with a weight evolution below the 3rd percentile despite adequate caloric intake. Normal liver transaminases, FIX and protein S. Ceruloplasmin was markedly reduced; FXI, protein C and AT were slightly decreased.

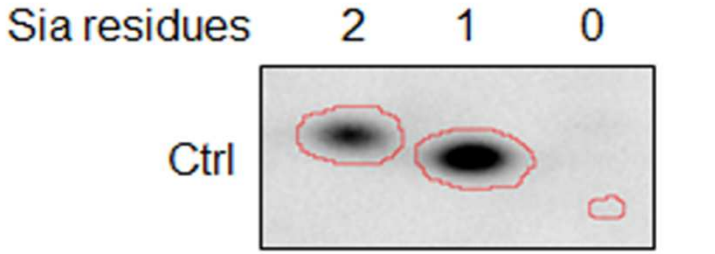
==> **CDG screening** using capillary electrophoresis (CE) of transferrin (Tf)

Capillary electrophoresis of transferrin

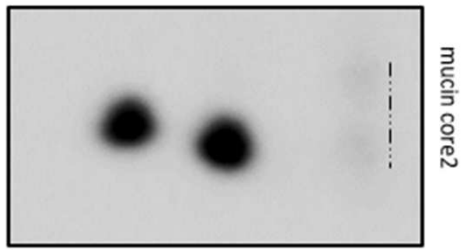


CDG-II pattern

2DE of apoC-III



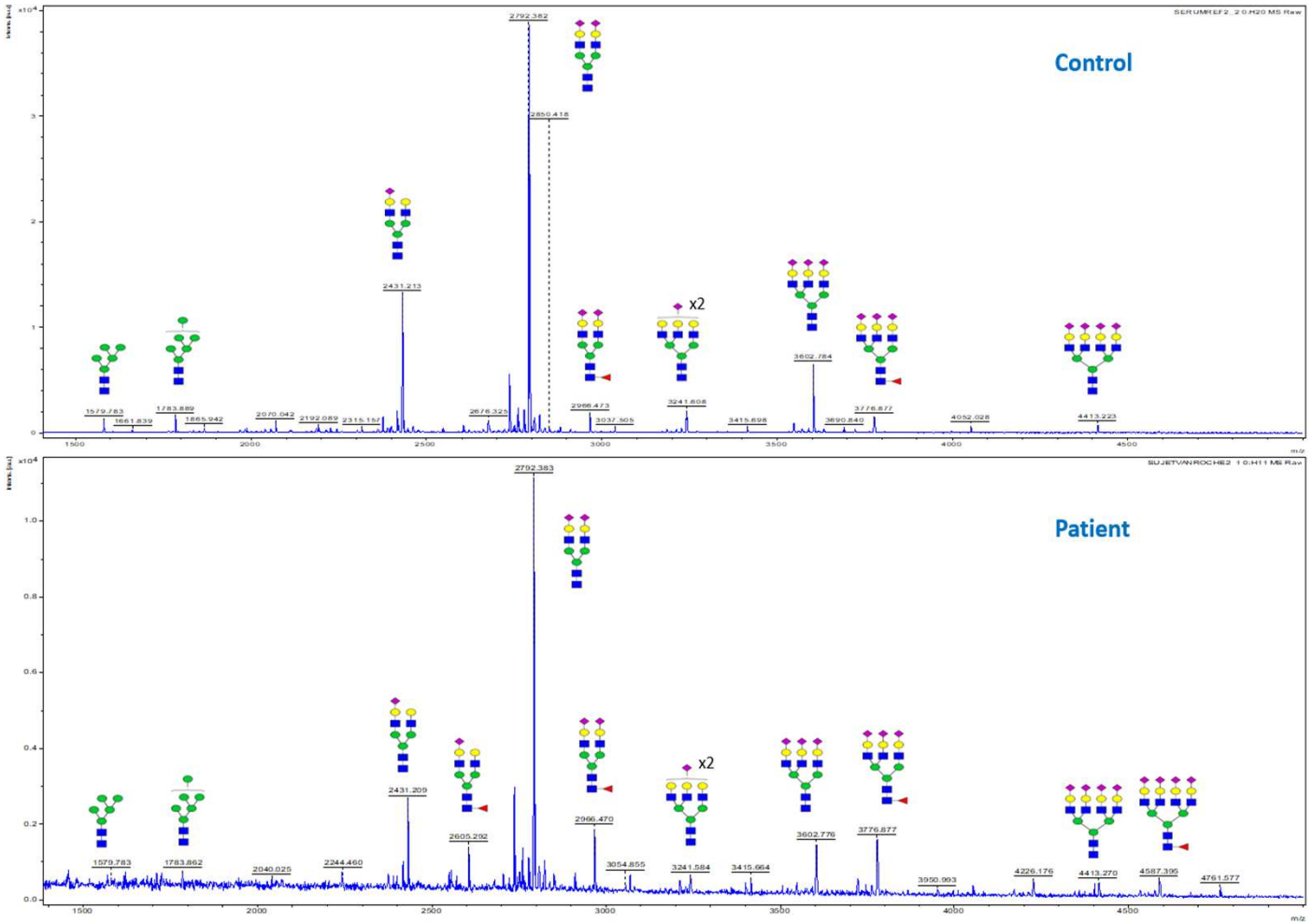
Normal % values :
- apoC-III$_2$: 25-60%
- apoC-III$_1$: 40-75%
- apoC-III$_0$: < 5%



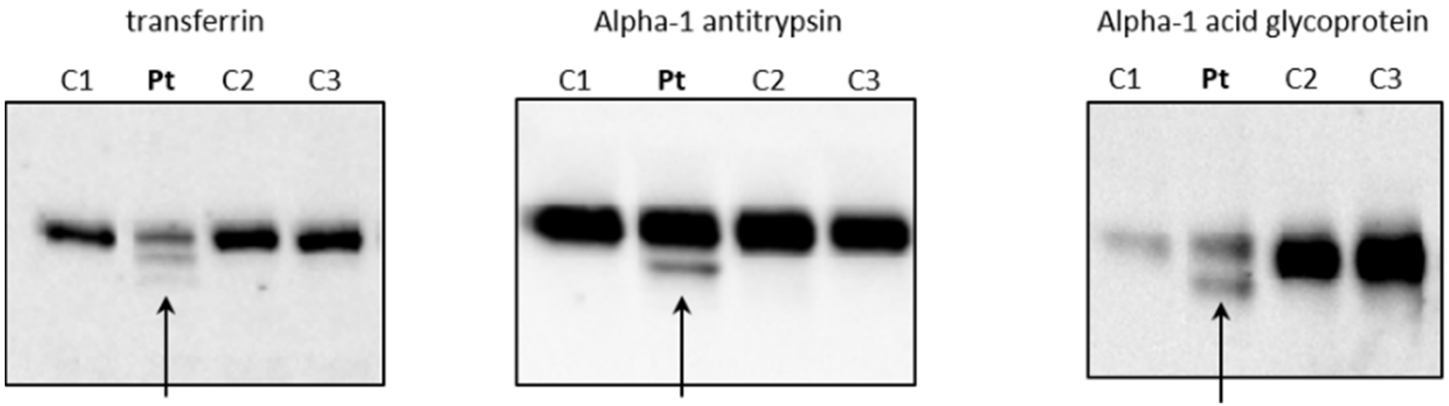
Patient
- apoC-III$_2$: 44%
- apoC-III$_1$: 56%
- apoC-III$_0$: 0%

Normal apoC-III pattern

MALDI-TOF of PNGase-released N-glycans



Western-blot of Tf, AAT and A1AGP

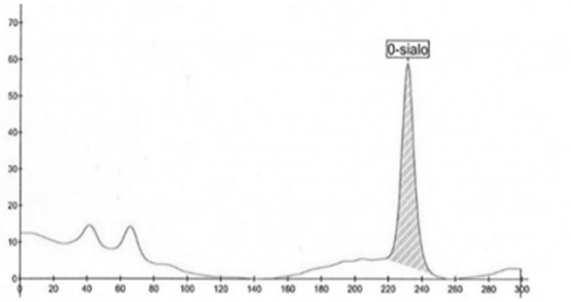


CDG-I patterns

Additional bands corresponding to the loss of entire normal N-glycan chains

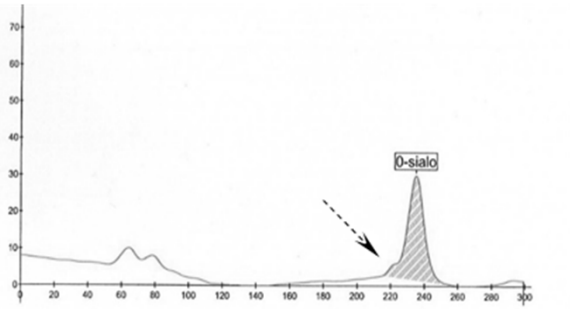
CDG-II? CDG-I?

CE of Tf after neuraminidase treatment

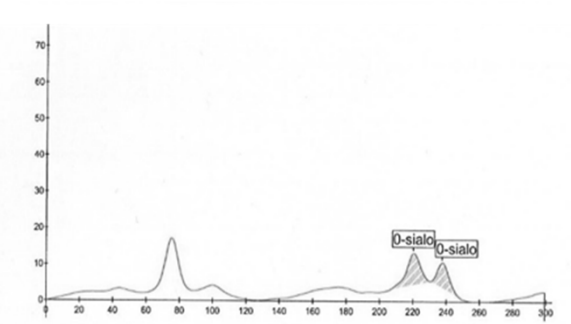


Control + neuraminidase

1 peak

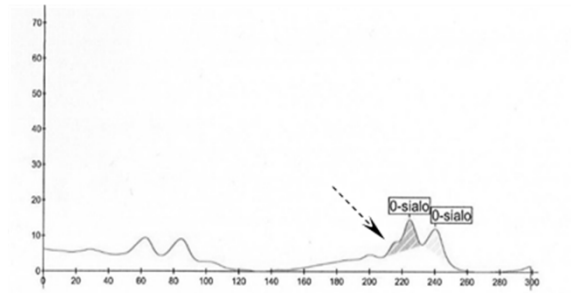


CDG-I + neuraminidase



Trf variant + neuraminidase

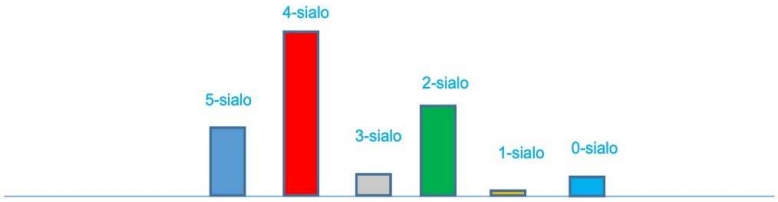
2 peaks



Patient + neuraminidase

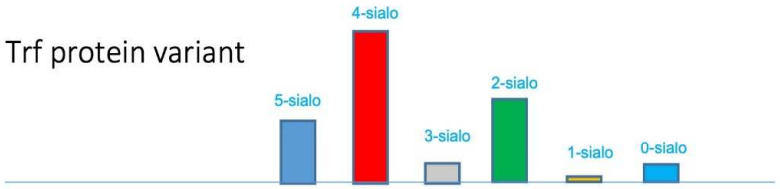
Tf protein variant

Interpretation

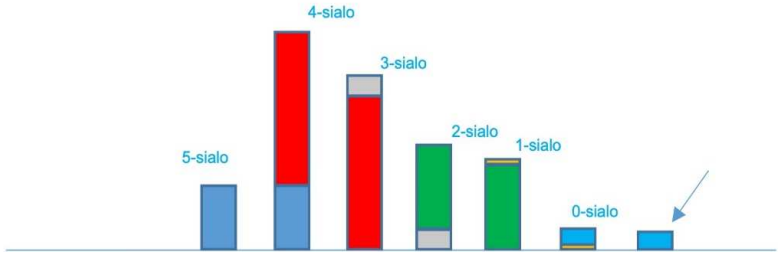


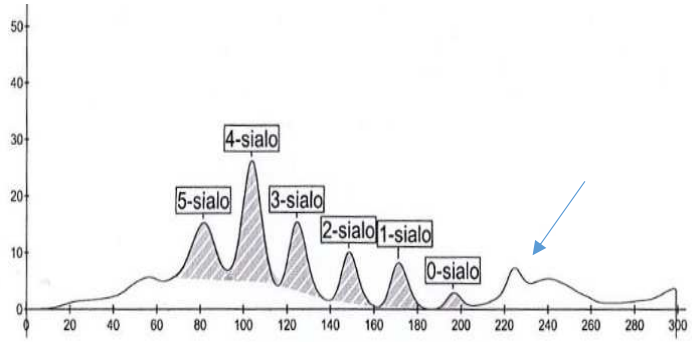
+

Overlay of two type 1 Tf patterns



CDG-I + Tf protein variant





Genetics

Direct Sanger sequencing

PMM2-CDG

c.317A>G (p.Tyr106Cys) and c.422G>A (p.Arg141His)

Conclusions

- First described case (?) of CDG combined with such a misleading transferrin variant
- Tf variant wrongly orientated towards CDG-II rather than CDG-I
- Interpret abnormal Tf patterns in relation with clinical signs and diagnostic hypotheses
- Neuraminidase treatment should be systematically (?) carried out on the discovery of a Tf pattern evocative of CDG

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