A too hasty and potentially fatal suspicion of CDG diagnosis: when genetics avoid a fundamental diagnostic mistake. Sweet ending

Élodie Lebredonchel[1], Alexandre Raynor[2], François Labarthe[3], Arnaud Bruneel[1,2], Violette Goetz[3]

[1] AP-HP, Biochimie Métabolique et Cellulaire, Hôpital Bichat, F-75018, Paris, France.

[2] INSERM UMR1193, Faculté de Pharmacie, Université Paris-Saclay, bâtiment Henri Moissan, 91400 Orsay, France.

[3] Centre de Référence des Maladies Héréditaires du Métabolisme ToTeM, Service de Médecine Pédiatrique, Hôpital Clocheville, Tours, France

elodie.lebredonchel@aphp.fr

Introduction

1) Case presentation

This report presents the case of a male newborn with consanguineous Afghan parents. The infant was discharged from the maternity ward on the third day of life and was receiving a mixed diet comprising human milk and formula. However, on the eleventh day of life, he was readmitted due to symptoms including vomiting, transient jaundice, hypotonia, and obstructive hydrocephalus, which was attributed to bilateral cerebellar hemorrhage of unknown origin. At one month of age, the infant developed fulminant hepatitis, together with hyperammonia, hyperlactatemia, and metabolic acidosis.

2) Admission assay

Initial infectious and metabolic screenings showed normal results. Neurological assessments did not reveal any abnormalities, however biochemical analyses indicated fulminant hepatitis without cholestasis:

- ↗ Aspartate transaminases (AST) 4199 U/L (N<31)
- ↗ Alanine transaminases (ALT) 2991 U/L (N<34)
- Hyperammonia 179 µmol/L (N<60)
- Metabolic acidosis (pH 7.06)) with ↗ anion gap
- Hyperlactatemia 10.1 mmol/L (N<2).

Several hemostasis parameters were disturbed:

- ↘ Prothrombin time (PTT) 57 % (N>70 %)
- ↘ Factor V <5 % (N>70 %)
- ↘ Factor II 57 % (N>70 %)
- ↘ Factor XI 17 % (N>60 %)
- ↘ Factor XIII 27 % (N>60 %)
- ↘ Fibrinogen 0.84 g/L (N : 1.6-4 g/L)

→ Insufficient to explain spontaneous hemorrhages.

Furthermore, large-scale hemostasis investigations revealed multiple abnormalities including :

- ↘ Antithrombin III 28 % (N>70 %)
- ↘ Protein C 14 % (N >30 %)

→ Glycosylation study

Capillary electrophoresis (CE) of transferrin for the screening of glycosylation defects

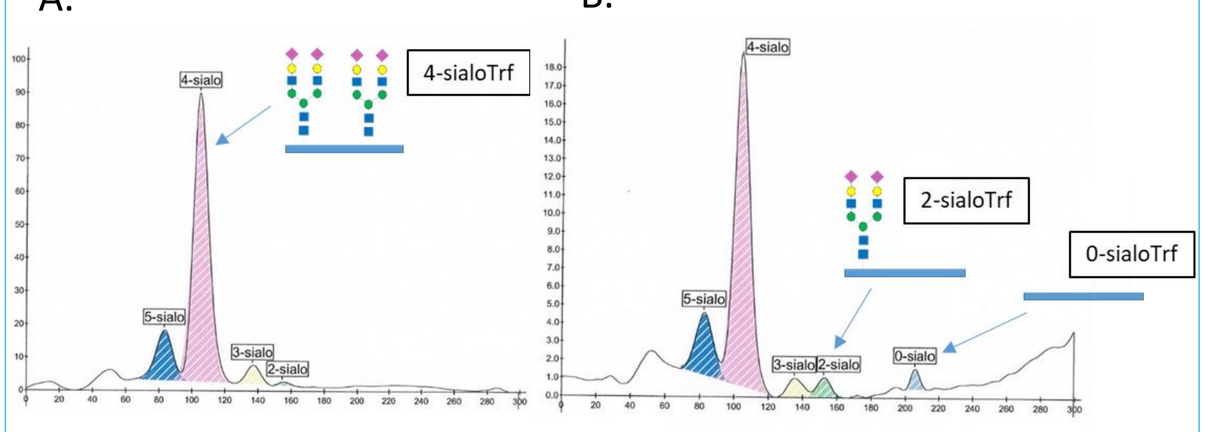

Figure 1: Transferrin glycosylation profiles of control serum (A) and patient (B)

A. A majority of 4-sialotransferrin. **B**. Compared to the control, the patient profile presents an increase of 2-sialotransferrin and 0-sialotransferrin fractions.

→ Evocative profil of a CDG type 1

Glycosylation defects study using Western Blot

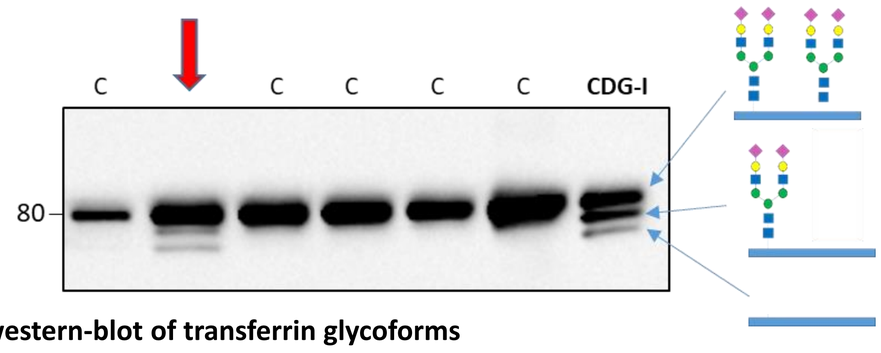

Figure 2: **western-blot of transferrin glycoforms**

Western-blot of transferrin from control samples (C), patient (bold arrow) and CDG-I (far right). Both the patient's profile and that of the CDG-I exhibit two additional bands indicative of the presence of glycoforms lacking complete *N*-glycan chains.

→ Confirms the results obtained using capillary electrophoresis

Genetic analysis

Screening for congenital disorder of glycosylation (CDG) was conducted, and the results were suggestive of mannose-phosphate isomerase deficiency (MPI-CDG or CDG-Ib), which can manifest as fulminant hepatitis, severe digestive issues, developmental delay, and coagulopathy. However, trio whole exome sequencing (WES) revealed a homozygous pathogenic variant in *ALDOB*, responsible for hereditary fructose intolerance (HFI or fructosemia), an inherited metabolic disorder with a favorable prognosis when managed with a fructose-free diet.

Typically, no clinical signs manifest prior to the introduction of solid food in infants.

Conclusion

HFI had not been previously evoked in view of the supposedly absence of diet diversification, but subsequent inquiry revealed that the parents systematically added white sugar to their child's bottle milk at home, leading to repeated and potentially life-threatening HFI decompensations.

Discussion

This case highlights the critical importance of a seamless collaboration between clinicians, biochemists and geneticists when confronted to severe and atypical presentations of inherited metabolic diseases. In this instance, both clinical and biological phenotypes initially pointed toward a CDG diagnosis, particularly MPI-CDG. However, without early WES, an erroneous diagnosis would have been made.

References

[1]N. Seta, A. Barnier, F. Hochedez, M.A. Besnard, G. Durand, Diagnostic value of Western blotting in carbohydrate-deficient glycoprotein syndrome, Clin Chim Acta. 254 (1996) 131–140. https://doi.org/10.1016/0009-8981(96)06379-6.

[2]F. Parente, N. Ah Mew, J. Jaeken, B.M. Gilfix, A new capillary zone electrophoresis method for the screening of congenital disorders of glycosylation (CDG), Clin Chim Acta. 411 (2010) 64–66. https://doi.org/10.1016/j.cca.2009.10.004.

[3]A. Čechová, R. Altassan, D. Borgel, A. Bruneel, J. Correia, M. Girard, A. Harroche, B. Kiec-Wilk, K. Mohnike, T. Pascreau, Ł. Pawliński, S. Radenkovic, S. Vuillaumier-Barrot, L. Aldamiz-Echevarria, M.L. Couce, E.G. Martins, D. Quelhas, E. Morava, P. de Lonlay, P. Witters, T. Honzík, Consensus guideline for the diagnosis and management of mannose phosphate isomerase-congenital disorder of glycosylation, J Inherit Metab Dis. 43 (2020) 671–693. https://doi.org/10.1002/jimd.12241.

[4]M. Tang, X. Chen, Q. Ni, Y. Lu, B. Wu, H. Wang, Z. Yin, W. Zhou, X. Dong, Estimation of hereditary fructose intolerance prevalence in the Chinese population, Orphanet J Rare Dis. 17 (2022) 326. https://doi.org/10.1186/s13023-022-02487-3.

[5]A. Davit-Spraul, C. Costa, M. Zater, D. Habes, J. Berthelot, P. Broué, F. Feillet, O. Bernard, P. Labrune, C. Baussan, Hereditary fructose intolerance: frequency and spectrum mutations of the aldolase B gene in a large patients cohort from France--identification of eight new mutations, Mol Genet Metab. 94 (2008) 443–447. https://doi.org/10.1016/j.ymgme.2008.05.003.

[6]S. Bijarnia-Mahay, S. Movva, N. Gupta, D. Sharma, R.D. Puri, U. Kotecha, R. Saxena, M. Kabra, N. Mohan, I.C. Verma, Molecular Diagnosis of Hereditary Fructose Intolerance: Founder Mutation in a Community from India, JIMD Rep. 19 (2015) 85–93. https://doi.org/10.1007/8904_2014_374.

[7]M. Gunduz, Ö. Ünal-Uzun, N. Koç, S. Ceylaner, E. Özaydın, Ç.S. Kasapkara, Molecular and clinical findings of Turkish patients with hereditary fructose intolerance, J Pediatr Endocrinol Metab. 34 (2021) 1017–1022. https://doi.org/10.1515/jpem-2021-0303.

[8]M. Ali, P. Rellos, T.M. Cox, Hereditary fructose intolerance, J Med Genet. 35 (1998) 353–365. https://doi.org/10.1136/jmg.35.5.353.

[9]T.M. Cox, Aldolase B and fructose intolerance, FASEB J. 8 (1994) 62–71. https://doi.org/10.1096/fasebj.8.1.8299892.

[10]B. Giguet, A. Bruneel, S. Vuillaumier Barrot, R. Moirand, E. Bardou Jacquet, Increased carbohydrate deficient transferrin: Whisky or candy?, JHEP Rep. 4 (2022) 100494. https://doi.org/10.1016/j.jhepr.2022.100494.

[11]E. Quintana, L. Sturiale, R. Montero, F. Andrade, C. Fernandez, M.L. Couce, R. Barone, L. Aldamiz-Echevarria, A. Ribes, R. Artuch, P. Briones, Secondary disorders of glycosylation in inborn errors of fructose metabolism, J Inherit Metab Dis. 32 Suppl 1 (2009) S273-278. https://doi.org/10.1007/s10545-009-1219-4.

[12]C. Wicker, C.-J. Roux, L. Goujon, Y. de Feraudy, M. Hully, A. Brassier, C.-M. Bérat, N. Chemaly, A. Wiedemann, L. Damaj, M.-T. Abi-Warde, D. Dobbelaere, A. Roubertie, A. Cano, A. Arion, A. Kaminska, S. Da Costa, A. Bruneel, S. Vuillaumier-Barrot, N. Boddaert, T. Pascreau, D. Borgel, M. Kossorotoff, A. Harroche, P. de Lonlay, Association between acute complications in PMM2-CDG patients and haemostasis anomalies: Data from a multicentric study and suggestions for acute management, Mol Genet Metab. 140 (2023) 107674. https://doi.org/10.1016/j.ymgme.2023.107674.

[13]T. Pascreau, C. Auditeau, D. Borgel, Hemostatic defects in congenital disorders of glycosylation, Res Pract Thromb Haemost. 7 (2023) 100142. https://doi.org/10.1016/j.rpth.2023.100142.

Hôpital Bichat Claude-Bernard AP-HP

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

SFBC Société Française de Biologie Clinique