Liver manifestations in a cohort of 39 patients with congenital disorders of glycosylation: pin-pointing the characteristics of liver injury and proposing recommendations for follow-up

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Background

The congenital disorders of glycosylation (CDG) are a heterogeneous group of rare metabolic diseases with multi-system involvement. The liver phenotype of CDG varies not only according to the specific disorder, but also from patient to patient. In this study, we sought to identify common patterns of liver injury among patients with a broad spectrum of CDG, and to provide recommendations for follow-up in clinical practice.

Methods

Patients were enrolled in the Frontiers in Congenital Disorders of Glycosylation (FCDGC) natural history study. We analyzed clinical history, molecular genetics, serum markers of liver injury, liver ultrasonography and transient elastography, liver histopathology (when available), and clinical scores of 39 patients with 16 different CDG types (PMM2-CDG, n=19), with a median age of 7 years (range: 10 months to 65 years). For patients with disorders which are treatable by specific interventions, we have added a description of liver parameters on treatment.

Results

Table 1 Patient characteristics and markers of liver injury

Patient	Age (Y)	Sex	CDG	Genotype	Protein change	ALT range	AST range	AlkP range
1	1	M	PMM2-CDG	c.44G>C; c.422G>A	p.Gly15Ala; p.Arg141His	15–145	10–147	172–301
2	1	M	PMM2-CDG	c.357C>A; c.422G>A	p.Phe119Leu; p.Arg141His	103–571	93–829	172–304
3	2	M	PMM2-CDG	c.357C>A; c.422G>A	p.Phe119Leu; p.Arg141His	53–1595	54–1222	222–464
4	3	M	PMM2-CDG	c.422G>A; c.691G>A	p.Arg141His; p.Val231Met	48–66	54–57	173–182
5	5	M	PMM2-CDG	c.422G>A; c.548T>C	p.Arg141His; p.Phe183Ser	34–41	23	186
6	5	F	PMM2-CDG	c.338C>T; c.710C>G	p.Phe113Leu; p.Thr234Arg	8–745	13–678	17–283
7	6	M	PMM2-CDG	c.357C>A; c.422G>A	p.Phe119Leu; p.Arg141His	25–1366	25–1986	115–1083
8	6	F	PMM2-CDG	c.415G>A; c.422G>A	p.Glu139Lys; p.Arg141His	19–31	31–48	157–250
9	6	M	PMM2-CDG	c.338C>T; c.422G>A	p.Pro113Leu; p.Asp148Asn	32–2524	26–4789	60–292
10	6	M	PMM2-CDG	c.422G>A; c.647A>T	p.Arg141His; p.Asn216Ile	37–71	45–69	104–155
11	7	F	PMM2-CDG	c.563A>G; c.691G>A	p.Asp188Gly; p.Val231Met	38–556	31–457	228–299
12	7	M	PMM2-CDG	c.205C>T;c.422G>A	p.Pro69Ser; p.Asp148Asn	28	42	225–242
13	8	M	PMM2-CDG	c.98A>C; c.140C>T	p.Gln33Pro; p.Ser47Leu	15–20	29–34	139–149
14	11	M	PMM2-CDG	c.422G>A; c.722G>C	p.Arg141His; p.Cys241Ser	17–18	25–26	154–172
15	12	M	PMM2-CDG	c.470T>C; c.710C>T	p.Phe157Ser; p.Thr237Met	44–68	46–58	187–240
16	15	M	PMM2-CDG	c.422G>A; c.458T>C	p.Arg141His; p.Ile153Thr	30–117	30–244	94–215
17	23	M	PMM2-CDG	c.26G>A; c.442G>A	p.Cys9Tyr; p.Asp148Asn	19–25	21–27	61–75
18	27	M	PMM2-CDG	c.357C>A; c.422G>A	p.Phe119Leu; p.Arg141His			
19	33	F	PMM2-CDG	c.357C>A; c.357C>A	p.Phe119Leu; p.Phe119Leu	14–164	21–327	44–48
20	31	M	ALG12-CDG	c.671C>T; c.1001delA	p.Thr224Met; p.Asn334ThrfsX15	18	23	61
21	46	M	ALG12-CDG	c.671C>T; c.1001delA	p.Thr224Met; p.Asn334ThrfsX15	15	22	121
22	1	F	ALG13-CDG	c.320A>G	p.Asn107Ser	10–18	40–49	102–165
23	4	F	ALG13-CDG	c.320A>G	p.Asn107Ser	17–49	28–51	118–405
24	59	M	DHDDS-CDG	c.124A>G; c.124A>G	p.Lys42Glu; p.Lys42Glu	25–27	37–38	77–82
25	63	F	DHDDS-CDG	c.124A>G; c.124A>G	p.Lys42Glu; p.Lys42Glu	20–27	28–33	69–82
26	2	M	PGM1-CDG	c.265G>A; c.988G>C	p.Gly89Arg; p.Gly330Arg	25	122	168
27	27	F	PGM1-CDG	c.206T>C; c.313A>T	p.Met67Arg; p.Lys105X	26–61	46–236	53–61
28	1	F	SLC35A2-CDG	c.340A>T	p.Lys114X	8–35	33–78	83–235
29	12	F	SLC35A2-CDG	c.815G>A	p.Trp272X	12–87	17–61	147–177
30	21	F	ALG6-CDG	c.998C>T	p.Ala333Val	12–50	17–51	81–275
31	8	M	ALG8-CDG	c.584T>C; c.1334T>C	p.Leu195Pro; p.Leu445Pro	20–165	14–148	73–275
32	65	F	DDOST-CDG	c.20C>G; c.1325T>A	p.Ala7Gly; p.Phe442Tyr	16–33	13–21	66–123
33	6	M	MPI-CDG	c.488-1G>C; c.656G>A	IVS4-1G>C; p.Arg219Gln	141–237	69–90	141–210
34	3	M	CCDC115-CDG	c.92T>C; c.92T>C	p.Leu31Ser; p.Leu31Ser	117–204	129–319	1071–1459
35	11	M	SLC10A7-CDG		Whole gene deletion (biallelic)	23	50–56	161–203
36	12	F	SLC35C1-CDG	c.503_505delTCT; c.942C>G	p.Phe168del; p.Tyr314X	17–29	19–29	211–273
37	2	M	SLC39A8-CDG	c.802C>T; c.802C>T	p.His268Tyr; p.His268Tyr	19–23	40–45	200–233
38	14	M	TMEM165-CDG	c.151C>T; c.725C>A	p.Gln51X; p.Thr242Lys	51–60	252–309	158–219
39	42	M	VMA21-CDG	c.52A>G	p.Arg18Gly*	24–48	39–62	113–160

Patients 20–21; 24–25 are siblings

Y years-old, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *AlkP* alkaline phosphatase, *M* male, *F* female. Age displayed is the current age. Normal ranges: ALT < 42 IU/L; AST < 41 IU/L; AlkP < 300 IU/L

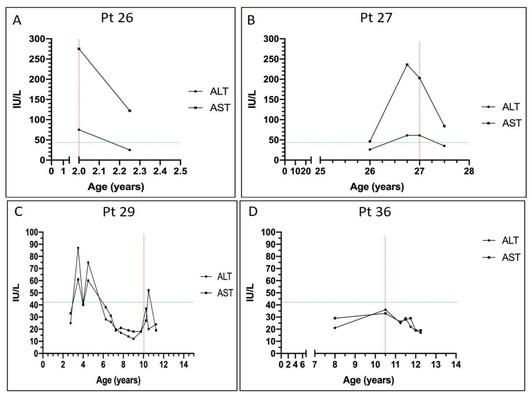

Figure 1: Evolution of ALT (circles) and AST (squares) values in treated patients. Red line = onset of treatment; green line = upper limit of normal. a, b Improvement after initiation of oral galactose therapy in two patients with PGM1-CDG; c mild transient elevation of aminotransferase values after initiation of oral galactose therapy in a patient with SLC35A2-CDG, with rapid normalization; d absence of significant change from a normal baseline after initiation of oral fucose therapy in a patient with SLC35C1-CDG

Results

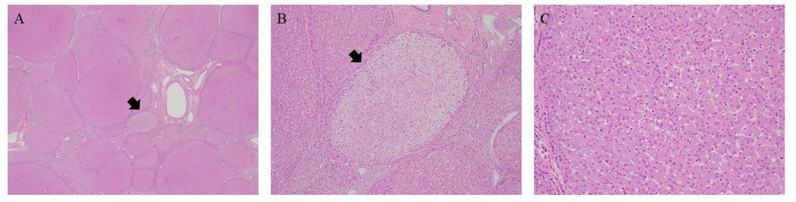

Figure 2: a. Liver, hematoxylin and eosin, 20 ×. Cirrhotic liver tissue with extensive bridging and enlarged portal tract. There is focal glycogen deposition in the cytoplasm of hepatocytes of a nodule (black arrow). **b.** Liver, hematoxylin and eosin, 200 ×. Hepatocellular nodule with cytoplasmic glycogen deposition (black arrow). **c.** Liver, hematoxylin and eosin, 200 ×. Hepatocellular nodule with discrete macrovesicular steatosis

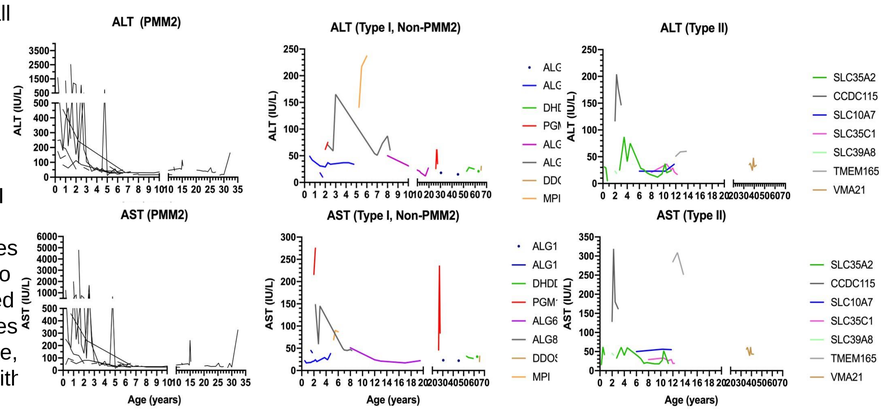

Figure 3: Aminotransferase values in all CDG patients according to type (**a** ALT values in PMM2-CDG patients. **b** AST values in PMM2-CDG patients. **c** ALT values in non-PMM2-CDG CDG-I patients. **d** AST values in non-PMM2-CDG CDG-I patients. **e** ALT values in CDG-II patients. **f** AST values in CDG-II patients). There is a notable inflexion point around 5 years of age in the figures A and B, after which most values tend to be normal or near-normal. A less defined inflexion point can be noted in the figures C and D at approximately 8 years of age, although there are still many patients with elevated values after this age

Conclusion

- (1) There is a clear pattern in the evolution of alanine aminotransferase and aspartate aminotransferase according to age. The cholangiocellular injury marker gamma-glutamyltransferase is not elevated in most patients, pointing to an exclusive hepatocellular origin of injury; (2) there is a dissociation between liver ultrasound and transient elastography regarding signs of liver fibrosis; (3) histopathological findings in liver tissue of PMM2-CDG patients include cytoplasmic glycogen deposits; and (4) most CDG types show more than one type of liver injury.
- We recommend that all CDG patients have regular systematic, comprehensive screening for liver disease that includes physical examination (for hepatomegaly and signs of liver failure), laboratory markers of hepatocellular injury (serum alanine aminotransferase and aspartate aminotransferase), liver ultrasound (for steatosis and liver tumors), and liver elastography (for fibrosis).

Reference

1. Starosta, R. T., S. Boyer, et al. (2021). "Liver manifestations in a cohort of 39 patients with congenital disorders of glycosylation: pin-pointing the characteristics of liver injury and proposing recommendations for follow-up." Orphanet J Rare Dis 16(1): 20.