

CCDC115-CDG: clinical presentation and glycosylation study of two new adult cases

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INTRODUCTION

Congenital disorders of glycosylation (CDG) related to defects of Golgi apparatus homeostasis constitute an increasing part of these inherited diseases. Among them, Coiled-Coil Domain Containing 115 genetic deficiency (CCDC115-CDG) has been recently described (*Jansen JC et al. AJHG, 2016*) in patients sharing CDG type II profile associated with hepatosplenomegaly, neurological symptoms, elevated aminotransferases (ATs), elevated alkaline phosphatases (ALP), hypercholesterolemia and disturbed copper metabolism. We present clinical, biological and glycosylation-related data on two unrelated adult cases of CCDC115-CDG with features expanding the phenotype of this disease.

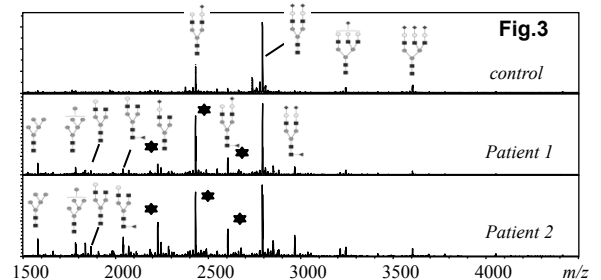
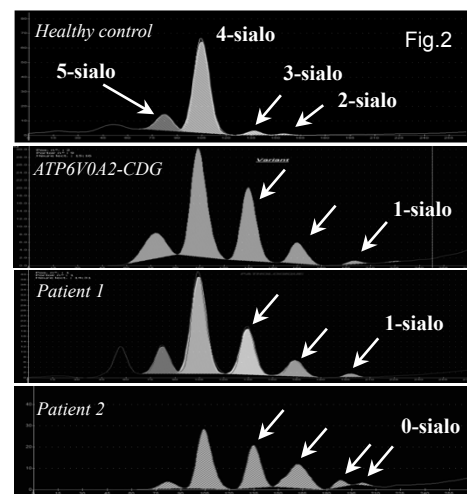
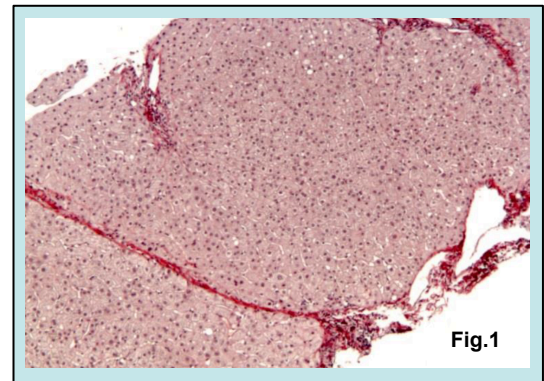
PATIENTS

Pt1 is a French girl from non-consanguineous parents. At birth, major hepatosplenomegaly (HSM) and cholestasis were reported. At 6 months of age, HSM was persistent but cholestasis normalized. Psychomotor development was mildly delayed. NPC disease was excluded. At 4 years of age, liver biopsy showed mild portal fibrosis without steatosis or iron overload. At 13 years of age, she had subnormal intellectual capacities and behavioral troubles. She showed persistent HSM and mild dysmorphic features. ATs and ALP were discreetly elevated while GGT, bilirubin and CK were normal. She had mild hypercholesterolemia. Metabolic investigations including plasma AA, urinary organic acids and lysosomal acid lipase were normal. Brain MRI was normal. Chromatographic analysis of the liver lipids showed high level of bis(MonoAcylGlycerol)phosphate. Additional findings were low serum copper and ceruloplasmin but Wilson disease (WD) was excluded. At 16 years of age, liver biopsy (**Fig.1**) showed mild portal fibrosis (F2) and heterogeneous steatosis.

Pt2 is a French man from non-consanguineous parents. No peculiar health problems were noted until 18 years old. At this time, serum analyses revealed elevated ATs and ALP, normal GGT, and elevated CK. No evident HSM was reported. Psychomotor development was normal without dysmorphic features. Liver biopsy showed severe fibrosis (F2-F3) with apparent biliary ducts regression. Biliary MRI did not evoke sclerosis cholangitis. At 20 years old, biological abnormalities were all persistent with additional hypercholesterolemia, low serum copper, and low ceruloplasmin (highly suggestive of WD). Penicillamin treatment did not ameliorate copper metabolism and WD was genetically excluded.

GLYCOSYLATION AND MOLECULAR STUDIES

Because of the liver involvement, a CDG screening test was performed. The two patients strikingly shared very similar glycosylation defects. Capillary electrophoresis of transferrin showed CDG-II patterns (**Fig.2**) which were in good agreement with the MALDI-TOF profiles of total plasma N-glycans (**Fig.3**), indicating accumulation of partially sialylated biantennary N-glycans and of N-glycans lacking both sialic acid and galactose. MALDI-TOF MS of O-glycosylated apoC-III also showed similar sialylation defects. Lastly, mutations (c.92T>C p.Leu31Ser/ c.19C>T p.Arg7* and c.92T>C p.Leu31Ser/ c.38T>C p.Leu13Pro) were found at the composite heterozygous state in exon 1 of *CCDC115* gene for both patients.



CONCLUSIONS

We present two CCDC115-CDG patients sharing routine biological data, copper-related parameters (highly suggestive of WD) and glycosylation anomalies. Patient 1 symptoms are similar to the first described patients, while patient 2 presents with severe liver fibrosis at adult age, with absence of HSM, of dysmorphia and of neurological involvement, expanding the clinical spectrum of CCDC115-CDG. Thus, we strongly recommend CDG screening in all patients with unexplained liver fibrosis associated with hypercholesterolemia, elevated ALP, and "WD-like" disturbed copper metabolism.