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CONGENITAL AFIBRINOGENAEMIA AND FAMILIAL COMBINED HYPERLIPIDAEMIA IN A KINDRED

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We studied the correlation of fibrinogen and plasma lipids in a 9 months old Jordanian girl with afibrinogenaemic proposita. The study design was a pedigree analysis composed of three generations, and 31 individuals. Age, gender, plasma fibrinogen, total cholesterol, triglycerides, LDL-cholesterol was measured. Our proposita plasma fibrinogen was absent; in addition to hyperlipidaemia type IIa. Her father's phenotype was IIb, and mother's was type IV. The family phenotypes were consistent with familial combined hyperlipidaemia.

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Fibrinogen (Fg) is important in blood clotting following its conversion to fibrin by thrombin. Fibrin monomers polymerize in the presence of fibrin stabilising factor XIII, thus stabilising the fibrin clot. Fg is composed of three pairs of polypeptide chains (à, ل and ç) covalently linked at their amino terminal portions, forming a central area called the E domain; were thrombin acts. The carboxy terminal portions of ل and ç chains form the terminal D domain. The genes for all three constitutive polypeptide chains of Fg are found in close proximity on chromosome 4[1].

Congenital afibrinogenaemia is a rare coagulation disorder characterized by the absence of plasma Fg measured by both clottable and immunologic assays[2]. In 1981, Girolami et al demonstrated a double hereditary pattern for congenital afibrinogenaemia, one autosomal recessive and the other autosomal intermediate[3].

Presentation in the neonatal period includes excessive bleeding from the umbilical cord, continued bleeding following circumcision, recurrent mucocutaneous haemorrhages, but not as severe as the intramuscular or intra-articular bleeding typically associated with classic haemophilia.

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As opposed to afibrinogenaemia, dysfibrinogenaemia represents the presence of a functionally abnormal Fg. Most individuals are either asymptomatic or suffer a mild-to-moderate haemorrhagic disorder; however, about 10 % are associated with thrombosis[4]. The confirmation of the diagnosis require discordant of functional Fg and its antigen concentration.

We report a 9 month old Jordanian girl discovered to have absent Fg on routine coagulation studies because of a right thigh ecchymoses associated with a raised total cholesterol and triglycerides levels. Investigation of three-generation relatives was undertaken to determine abnormalities of Fg, total cholesterol (TC), triglycerides (TG) and LDL-Cholesterol (LDL-C) and this showed a pattern consistent with familial combined hyperlipidaemia (FCHL).

In addition, the raised Fg level among hyperlipidaemics as compared to normolipidaemics, suggest a possible role of lipids in Fg metabolism.

METHODS

Fg was measured by precipitation and functionally by thrombin clottable Fg[5]. Enzymatic methods standardised by the Center for Disease Control (CDC) in Atlanta, Georgia using the Abell-Kendall method were employed to quantify plasma total cholesterol and triglyceride levels with Abbott VP Super System Analyser, Abbott Laboratories, and Irving, Texas, USA. Agarose electrophoresis was performed on 0.5 % agarose gel in 60 mmol/L of barbital buffer, at a pH of 8.6 for 3 hours at 50 V 150 mA, visualised by trichloroacetic acid.

Family Under Study

A 9 month old Jordanian girl was referred to our hospital because of right thigh ecchymoses. She was the product of a full term normal vaginal delivery. No history of abnormal umbilical cord stump exsanguination, or haemorrhage at ear piercing. No bruising or significant haemorrhagic episodes during infancy. Her initial coagulation screen revealed a thrombin time (TT) (normal < 17 seconds), activated partial thromboplastin time (APTT) (normal 22-37 seconds), and prothrombin time (PT) (normal 9-12 seconds) were all greater than 100 seconds. Reptilase time (RT) 40 seconds (normal 13-16 seconds). All the aforementioned tests were corrected with control plasma. Clottable Fg was absent (normal 1.5-3.5 g/L) and no Fg could be detected by immunoprecipitation confirming the complete absence of Fg. An agarose gel electrophoresis visualised by trichloroacetic acid precipitation (Fig 1) showed absent Fg from the patient plasma. A prominent Fg band was found in the control plasma protein electrophoresis of her parents between ل and ç region (Fig 1). An interesting feature was the prolonged bleeding time (BT) (Ivy template) of 10 minutes (normal 3-8 minutes) in the absence of thrombocytopenia, denoting platelets aggregation abnormality (platelets aggregation by ADP was 40 %, normal > 70 %), which did correct with the addition of fresh frozen plasma (FFP). Local therapy with ice packs and limiting her activity, in addition to FFP controlled the bleeding.

The parents were not related, and were asymptomatic regarding excessive bleeding. Their BT, PT, APTT, TT, RT and platelets aggregation studies were normal. Assays of parental Fg were; father 3 g/L, mother 2.8 g/L (normal 1.5-3.5 g/L). Absence of Fg from the patient plasma with normal parental values suggests autosomal recessive inheritance. The mean Fg levels in the normolipidaemic individuals were comparable to a reference population[6], while the mean Fg levels in the hyperlipidaemic individuals were raised.

Because of increased incidence of coronary heart disease among the family of our patient, and considering Fg and hyperlipidaemia as risk factors for increased cardiovascular morbidity and mortality, a three-generation family study was undertaken (Fig 2). A total of 23 individuals have been studied, including all living grand parents, parents and parental siblings. On the paternal side all members were asymptomatic regarding excessive bleeding tendencies, two members (1-1, II-1) are known to have had myocardial infarction at the ages of 65, 54 respectively. On the maternal side all members were also asymptomatic regarding excessive bleeding tendencies, three members (1-3, 1-4, II-8) were known to have had myocardial infarction at the ages of 58, 55, 45 years respectively, one of which was fatal (1-3) at the age of 58 years.

The results of the lipid studies were classified according to the WHO Classification of Hyperlipidaemias7 and were as follows: phenotype IIa raised (TC/LDL-C) and normal TG (1-1, II-2, III-2, III-6); phenotype II_b raised (TC/LDL-C/TG) (II-1, II-4, II-8, III-15); phenotype IV, normal (TC/LDL-C), raised TG, phenotype V, normal (LDL-C) raised (TC/TG) (III-a, III-8, II-5, III-10, III-14). Father's phenotype was II_b while her mother's phenotype was IV. The results of the 23 individuals studied in the family are shown in Table 1.

Table 1. The age, gender, fibrinogen, total cholesterol, LDL cholesterol and triglycerides values according to the WHO classification for lipids in addition to the mean value for each group

	Age/Sex Year	Fibrinogen 1.5-3.5 g/L	Total Ch <5.2 mmol/l	TG <1.8 mmol/L	LDL-Ch 1.3-4.9 mmol/L
Patient III-9	9 months	0	6.12	1.22	5.09
Hyperchole sterolaemia (Type IIa), n=4					
I-1	76y/M	3.6	7.16	2.63	5.81
II-2	58y/M	4.0	9.77	1.81	8.04
III-2	34y/M	3.8	18.04	2.00	15.22
III-6	29y/M	3.3	13.54	2.11	11.32
MeanŚD	49	10.10ˊ4.10	2.14ˊ0.35	12.13ˊ4.73	3.68ˊ0.3 22ˊ
Hypertrigly ceridaemia (Type IV/V), n=5					
II-5/Mother	22y	2.8	4.65	3.16	3.7
III-1	36y/F	4.1	3.31	2.20	2.64
III-8	14y/M	3.8	4.34	2.45	3.72
III-10	28y/F	3.6	3.05	2.12	2.25
III-14	4y/F	2.7	2.66	2.45	2.14
MeanŚD	21	2.89ˊ0.77	2.48ˊ0.41	3.60ˊ0.85	3.4ˊ0.62 14ˊ
(Type IIb), n=4					
II-1	60y/M	3.8	11.68	2.46	9.84
II-4/father	28y	3.0	6.56	4.52	4.63
II-8	58y/M	4.2	9.51	8.69	8.06
III-15	42y/M	3.6	8.53	6.84	7.70
MeanŚD	47	7.56ˊ2.16	5.63ˊ2.71	7.93ˊ2.50	3.65ˊ0.5 15ˊ
Normolipaemic n=10					
I-2	72y/F	3.8	4.32	1.73	3.18
II-3	48y/F	3.5	5.71	1.69	4.67
II-6	52y/M	4.6	4.65	2.36	3.36
II-7	37y/M	3.0	4.42	1.39	2.79
III-3	33y/M	3.6	4.57	1.59	1.55
III-4	31y/F	3.8	6.15	1.71	4.39
III-5	27y/M	3.1	3.18	1.25	2.27
III-7	20y/F	3.0	4.65	1.29	4.08
III-12	8y/M	3.0	3.18	1.10	2.09
III-17	35y/M	3.0	5.50	1.29	4.44
MeanŚD	36	3.28ˊ1.10	1.54ˊ0.36	4.63ˊ0.98	2.43ˊ0.49 18ˊ

DISCUSSION

In our report, we describe the coexistence of two genetic disorders in kindred, one related to Fg and the other to lipids.

Fg levels are controlled by an interaction between genetic and environmental factors[8]. Genetic control in normal individuals has been reported to range from as low as 15 % to as high as 51 %[9]. In afibrinogenaemia, the genetic defect is not due to an abnormality of the fibrinogen gene since copy for all three peptides has been reported to be present and grossly intact[10]. Consequently, the failure to synthesise/secrete Fg may be due to transcription, translation, and/or secretory defects.

A presumptive diagnosis of FCHL was made based on the demonstration of multiple phenotypes within the same family. Lipoprotein kinetic studies have indicated that high production rates of very low density lipoprotein (VLDL) and apolipoprotein B (apo-B) from the liver or abnormal 'metabolic channeling' in the circulation may underlie FCHL.

In addition, the AI-CIII-AIV gene cluster is the major locus for FCHL, and that mutation of the X2 allele found in half of all patients with FCHL accounts for the metabolic disorder[11]. The mean Fg levels in the hyperlipidaemic individuals were raised, as opposed to normal mean Fg levels in the normolipidaemic population. Fg levels correlated with TC in an epidemiological study[12], also showed raised Fg in hyperlipoproteinaemia (HLP) type II[13].

CONCLUSION

The association of two independent risk factors for coronary artery disease is described in kindred. The mean fibrinogen levels in hyperlipidaemic phenotypes were raised, while the mean fibrinogen levels in normolipidaemic were comparable to a reference population.

The mode of inheritance for familial combined hyperlipidaemia is dominant with reduced penetrance. The hereditary transmission of afibrinogenaemia is suggestive of autosomal recessive pattern. It may be possible to speculate on the possible protective role for hyperlipidaemia in patients with low fibrinogen levels.

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