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HLA investigations in cardiomyopathies

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Typization of HLA A, B and C antigens of peripheral lymphocytes was performed in 14 patients suffering from cardiomyopathy and in 10 family members from 10 families. Among the antigens of locus A, the most frequent were the subgroups of HLA A9 (A23 and A24) in 7/14, and those of HLA A10 (A25 and A26) in 3/14; frequent antigens of locus B were the types B5, B7, B12 and B35. In 2 of 10 families the cardiomyopathy was transmitted by autosomal dominant genes, while the other cardiomyopathy cases were sporadic.

The HLA B8 antigen was not observed in any case of cardiomyopathy.

The familial occurrence of idiopathic cardiomyopathy (CMP) was described by Evans [5] while others differentiated "familial" and "nonfamilial" cases [1, 4, 9, 15, 16]. In some families inheritance by an autosomal dominant gene has been suggested [2, 3, 6, 17]. Emanuel et al [7] demonstrated both dominant and recessive modes of transmission in families with idiopathic CMP.

Suggested aetiological causes include embryonic growth disturbance, increased catecholamine effect, a primary disorder of myocardial metabolism, hypertension preceding the development of CMP, abnormal contraction towards the end of isometric contraction during development, small vessel disease, and the role of the histocompatibility antigen (HLA) system [19]. The genetic basis of the disease is well-established and may closely be associated with the HLA-antigen system. Patients with HLA B12 or HLA A23 are hypertensive and have a family history of CMP. HLA DRw4 was found in 73% of patients with hypertrophic cardiomyopathy as compared with 33% in normal controls [12].

The aim of the present study was a genetic analysis of CMP families and the determination of HLA antigens.

Investigated Families and Methods

HLA A, B and C antigens were studied in 14 CMP patients, mostly children, and 10 family members. As

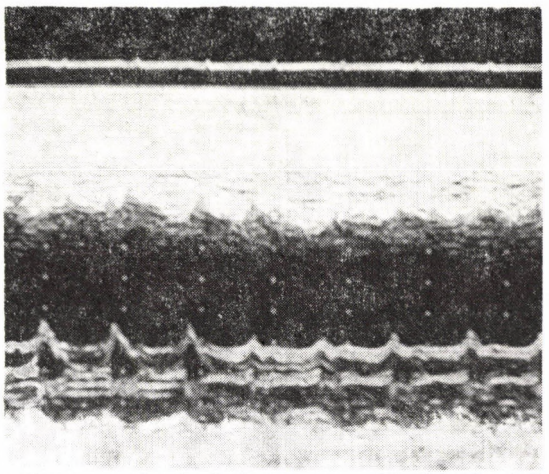

FIG. 1. Congestive cardiomyopathy in O. I. ten-year-old girl. The left ventricular cavity is extremely large with small posteriorly displaced mitral motion

a control group the occurrence of HLA antigens was studied in 222 healthy blood donors. Typing for HLA–A, B and C antigens was done by means of standard NIH lymphocytotoxicity test [4] with lymphocytes taken from peripheral blood.

Evaluation was made by the X^2-test.

REPORTS OF CASES

Case 1 (I/1) O. I., a 10 years old girl had first been observed at the age of 5 years with severe circulatory failure. There was no indication of an acute inflammatory disease, and congenital heart defect could be excluded on the basis of angiographic examination and heart catheterization. All four cavities of the heart were dilated, ventricular end-diastolic pressure was elevated. Prednisolone therapy proved to be ineffective. Digitalisation and treatment with diuretics prevented progression of the disease. On the basis of chest X-rays, electrocardiography and echocardiography congestive cardiomyopathy (COCM) was diagnosed (Fig. 1).

Case 2 (II/1) V. K., a 6 years old girl had been known to suffer from CMP since infancy. The first symptoms of obstructive CMP (HOCM) became conspicuous and verapamil (calcium antagonist) treatment was introduced. At the age of 4 years pulmonary circulatory failure accompanied by cardiomegaly ensued. Echocardiography showed enlarged left atrium and ventricle, hypokinetic left ventricle and moderate thickening of the ventricular septum, i.e. signs characteristic of obstructive CMP (HOCM). Electrocardiography disclosed WPW syndrome of the B type. Treatment with digitalis was introduced.

The girl's mother (II/2) and her maternal aunt (II/3) had WPW syndrome, and in addition the latter displayed supraventricular tachycardia on several occasions. In the family autosomal dominant inheritance of COCM was proved.

Case 3 (III/1) K. N., a 14 years old girl had first been examined at the age of 9 years because of fatigue. Moderate cardiomegaly with proper myocardial function had been diagnosed.

At age of 13 years she had reported of increasing fatigue and fear of death. Chest X-rays and echocardiography (ECG) indicat-

ed cardiomegaly and moderate pulmonary congestion. ECG showed slightly enlarged left atrium and left ventricle and decreased contractility. So, COCM was diagnosed.

The girls father (III/5) and the father's sister (III/4) suffer from COCM. Two brothers (aged 32 and 44 years) and one sister (aged 36) died with COCM. Another brother of the father, aged 50, and having a pacemaker, also suffers from COCM. Autosomal dominant inheritance has been proven.

Case 4 (VII/1) A. I., a 3 years old boy. A few days after birth a slight systolic murmur had been noted; severe circulatory failure had ensued. Heart catheterization had revealed a coarctation syndrome (coarctation of the aorta, patent duct, ventricular septal defect) and emergency cardiac surgery had been performed (duct ligation. resection and end-to-end anastomosis). During the postoperative period a severe postcoarctectomic syndrome developed with hypertension and hypertensive encephalopathy (blood pressure: 260 mm Hg). In infancy the patient was treated several times because of severe heart failure. Heart catheterization performed at the age of 2 years failed to reveal VSD, presumably because the duct had closed. The outflow tract was, however, narrowed, the septum bulged into the left ventricle. Thus, heart catheterization indicated the presence of HOCM. M-mode echocardiography showed septum hypertrophy, the septum/posterior wall ratio was greater than 1.3. The diagnosis of HOCM presumably of the secondary type was supported by ECG examination.

After verification of the diagnosis, digitalisation was discontinued and treatment with calcium antagonists was introduced which resulted in a compensated or subcompensated circulation.

Results

Table I shows the HLA antigens and the haplotypes, the clinical forms of CMP cases and the types of inheritance. Of 14 CMP patients 5 had HLA A24 antigen, other 2 patients had HLA A23 antigen; both of them being subgroups of HLA A9 antigen.

The subgroups of HLA A10 are the HLA A25 and A26 antigens. The HLA A25 antigen was detected in 1 CMP and A26 antigen was detected in 2 cases, so the HLA A10 antigen occurred in 3 patients.

The related antigens of the B group B5 (n = 4), B12 (n = 3), B40 (n = 2), B49 (n = 2), B35 (n = 3) and B7 (n = 3) were observed. B5, B7 and B12 antigens were not found in our two cases with HOCM (II/1, VII/1). Two of 10 families with CMP cases showed autosomal dominant heredity with the subgroups of HLA A9 antigen and with B5, 49 and 35. V. K. (II/1) and her mother (II/2) showed HLA identity for haplotype HLA A2/B40. In the other CMP family with autosomal dominant transmission, the 3 CMP patients (III/1, III/4, III/5) had the same antigen B5, while two healthy family members (III/2, III/3) had not this one, so antigen B5 was a discriminating factor between the affected and the healthy persons.

Discussion

Recent reports have suggested that a possible explanation for a symmetric hypertrophy of the interventricular septum (ASH) was an underlying liability and that some individuals with ASH develop cardiomyopathy. This model is polygenic, involving thresholds for both ASH and hypertrophic cardiomyopathy [8].

TABLE I

HLA and genetical data of CMP families

Sign	Sex	HLA-A		B		Cw	HLA-haplotype	Dg	Heredity
I/1 O. I.	♀ affected	2,	24	12,	41	4	2—12/24—41/4	COCM	non-familial
I/2 O. I.	sister	2,	2	12,	12		2—12/2—12		
I/3 O. F.	father	2,	24	12,	41	4	—		
I/4 Mrs. O.	mother	2,	2	12,	12		2—12/2—12		
II/1 V. K.	♀ affected	2,	23	40,	49	6	2—40/23—49/6	HOCM	AD
II/2 Mrs. V.	affected mother	2,	11	35,	40	3, 6	2—40/11—35	COCM, WPW	
II/3 Mrs. K.	affected maternal aunt	3,	11	5,	35	6	3—5/11—35	COCM, SVT WPW	
III/1 K. N.	♀ affected	2,	24	13,	5		2—13/24—5	COCM	AD
III/2 K. M.	healthy sister	1,	24	8,	18	6	1—8/24—18/6		
III/3 K. Zs.	healthy sister	23,	24	18,	18	6	23—18/24—18/6		
III/4 Mrs. H.	affected paternal aunt	2,	3	5,	7		2—5/3—7	COCM	
III/5 K. L.	affected father	2,	24	5,	18		24—5/2—18	COCM	
IV/1 Mrs. S.	affected	23,	26	12,	22	3, 6		COCM	non-familial
V/1 K. Z.	♂ affected	1,	26	49,	49			COCM	non-familial
VI/1 R. K.	♂ affected	2,	24	17,	13		24—13/2—17	COCM	non-familial
VI/2 Mrs. R.	healthy	2,	24	13,	15				
VII/1 A. I.	♂ affected	1,	31	14,	35			HOCM	non-familial
VIII/1 Cs. I.	♀ affected	2,	25	7,	29			COCM, ES	non-familial
VIII/2 Cs. M.	healthy sister	2,	33	38,	41			ES	
VIII/3 Mrs. Cs.	healthy	2,	25	38,	29				
IX/1 K. Zs.	♂ affected	2,	2	12,	12			COCM	non-familial
X/1 A. A.	♂ affected	24,	28	7,	22		24—22/28—7	COCM	non-familial
X/2 Mrs. A.	healthy mother	2,	24	18,	22				
X/3 Mr. A.	healthy father	3,	28	7,	22				

COCM = congestive cardiomyopathy
HOCM = obstructive cardiomyopathy
ES = extrasystole
WPW = Wolf-Parkinson-White
SVT = supraventricular tachycardia
AD = autosomal dominant

There is evidence for linkage between certain HLA haplotypes and hypertrophic CMP in some families.

Genetic dominance can be shown when an enzyme in a biological pathway is rate-limiting. The receptors are mutant. Two types of taurine receptor can be identified [18]. Structural proteins are affected. Sarcolemmal membrane involvement resulting in an abnormal proportion of various constituents has been reported [11]. An autosomal recessive mode of transmission in the cases of familial hypertrophic CMP has also been reported [7].

Two of 10 CMP families showed autosomal dominant heredity, while the other CMP cases were sporadic. ASH was revealed by echocardiography in one of our cases (VII/1) without any sign of polygenic transmission.

Fiorito et al [8A] found HLA DR3 antigen linkage in patients with HOCM. Typing of DR antigens has not been performed by us.

The two subgroups of HLA A9 (HLA A23 and A24) were detected in 7 of our 14 CMP cases. HLA B8 antigen had not been observed in our CMP cases, so that seems to be a negative correlation. HLA B8 antigen was the most frequent among healthy donors and in alcoholic CMP cases [10].

References

1. Braunwald E, Lambrew CT, Rockoff SD, Ross J, Morrow AG: Idiopathic hypertrophic subaortic stenosis. I. A desciption of the disease based upon an analysis of 64 patients. Circulation 30, Suppl. 4, 3, 1964.
2. Brigden W: Uncommon myocardial disease. The non-coronary cardiomyopathies. Lancet 2:1179, 1957
3. Brent LB, Aburano A, Fisher DL, Moran TJ, Myers JD, Taylor WJ: Familial muscular subaortic stenosis: an unrecognized form of "idiopathic heart disease", with clinical and autopsy observations. Circulation 21:167, 1960
4. Davies LG: Familial heart disease. Br Heart J 14:206, 1952
5. Evans W: Familial cardiomegaly. Br Heart J 11:68, 1949
6. Emanuel R: A classification for the cardiomyopathies. Am J Cardiol 26: 438, 1970
7. Emanuel R, Withers R, O'Brien K: Dominant and recessive modes of inheritance in idiopathic cardiomyopathy. Lancet 2:1065, 1971
8. Emanuel R, Withers RFJ: Genetics of the cardiomyopathies. Progress in Cardiology (in press)

8/a. Fiorito S, Autore C, Fragola PV, Purpura M, Cannata D, Sangiorgi M: HLA-DR3 antigen linkage in patients with hypertrophic obstructive cardiomyopathy. Am Heart J 111:91, 1986

9. Hollman A, Goodwin JF, Feare D, Renwick JW: A family with obstructive cardiomyopathy (asymmetrical hypertrophy). Br Heart J 22:449, 1960
10. Kaiser G, Hőgye M: personal information.
11. Matsumori A, Kawai C, Wakabayashi A, Terasaki PI, Park MS, Sakurami T, Ueno Y: HLA-DRw4 antigen linkage in patients with hypertrophic obstructive cardiomyopathy. Am Heart J 101: 14, 1981
12. Owens K, Weglicki WB, Ruth RC: Lipid composition, Ca^{2+} uptake and Ca^{2+}-stimulated ATP-ase activity of sarcoplasmic reticulum of the cardiomyopathic hamster. Biochim Biophys Acta 296:71, 1973
13. Schrader WH, Pankey GA, Davis RB, Theologides A: Familial idiopathic cardiomegaly. Circulation 24:599, 1961
14. Terasaki P: Manual of Tissue Typing Techniques. 4:50, NIH, Bethesda 1972
15. Treger A, Blount SG: Familial cardiomyopathy. Am Heart J 70: 40, 1965
16. Walther RJ, Madoff IM, Zinner K: Cardiomegaly of unknown cause occurring in a family. Report of three siblings and review of the literature. N Engl J Med 263:1104, 1960
17. Weber DJ, Gould L, Schaffer AI: A family with idiopathic myocardial hypertrophy. Am J Cardiol 17:419, 1966

18. Welty MC, Welty JD, McBroom MJ: Effect of isoproterenol and taurine on heart calcium in normal and cardiomyopathic hamsters. J Molec Cell Cardiol 14:353, 1982

19. WHO Expert Committee: Cardiomyopathies. World Health Organization, Technical Report Series, 697. Geneva 1984

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