The Pre-Excitation Syndrome: Epidemiological And Genetic Study

*ZIJAD DURAKOVIC**
*ASAF DURAKOVIC***
*and ANDRIJA KASTELAN****

Summary

A sample of 4210 subjects of both sexes aged 35-54 was examined, chosen at random from six regions of Croatia. An electrocardiogram at rest was performed in all subjects and changes analyzed by the Minnesota code. Forty-two (1.0%) of the examinees had a short P-R interval, while this finding together with a widening QRS complex and delta wave, was found in 0.05% of the examinees. During the period of the study, 0.35% of the subjects had a short P-R interval after three years, and of this number in 22% the finding had disappeared in three years. 13 years after the first examination, there were more short P-R intervals: 3.22% in females and 1.96% in males. Three years after the first examination 0.06% of the subjects had pre-excitation with a delta wave, and it appeared in one subject after three years. After 13 years those subjects did not appear for an examination, and the finding did not appear in any of other subjects during this period.

Antigens of the HLA system were analyzed in 46 patients: WPW was found in 35 while 11 had LGL syndrome. Antigens of the HLA-A, HLA-B and HLA-DR locuses were determined by the microlymphocytotoxicity method. The results of the frequency of HLA system antigens were compared to the results in a Croatian population. There is increased frequency of HLA-A9 and HLA-B5 (p=0. 026 and 0.0092) in the investigated population as a whole. The participation of HLA-A3 antigen is significantly less among patients (p=0.003), while the HLA-B14 antigen was not found in patients with pre-excitation (p=0.03). Within 10 HLA-DR locuses, HLA-DR7 antigen was rather more frequently present, although this was not statistically significant (p=0.173).

Introduction

Pre-excitation occurs because during organogenesis accessory pathways are formed of the conducting musculature in the heart, by which impulses are spread to the ventricles, by-passing the pathways of normal conduction of stimulus by the atrioventricular node, which most frequently results in attacks of paroxysmal tachycardia or tachyarrhythmias[1-3]. There are 60 different hypotheses to explain this syndrome [4]. The type of conducting musculature can be systematized into five basic groups[2,3,5-8]: the first is Kent's bundle between the atria and the ventricle beside the atrioventricular node (in the ECG: short P-Q interval, widened QRS complex with a delta wave), the second is James' threads between the atria and the atrioventricular node (in the ECG: short P-Q interval), the third are threads between the atrioventricular node and ventricles (Mahaim's fibers), the fourth is the atrioventricular bundle and the fifth are the threads between His' bundle and the ventricles at the beginning or at the end. In the European group for pre-excitation, Anderson et al[9] proposed a classification of accessory

* Division of Cardiology, Department of Internal Medicine.
** Department of Nuclear Medicine, VA Regional Medical Center, Wilmington, Delaware, U.S.A.
*** Tissue typing Center, Rebro University Hospital, Medical Faculty University of Zagreb, Croatia. Yugoslavia.

threads of conducting musculature in the heart based on anatomic finding of the accessory pathways.

The prevalence of this finding in the general population is an open problem. According to our clinical analyses[10] WPW or LGL syndrome (first: short P-Q, widended QRS with delta wave and attacks of supraventricular tachycardia or tachyarrhythmias, second: short P-Q interval without widened QRS and with supraventricular tachycardia or tachyarrhythmias) were found in 87% of patients with pre-excitation.

In patients with the re-excitation syndrome the majority have no history of such disease in the family, although it is found in some patients[1,,12]. In some families it appears as an autosomal dominant inheritance[13], together with paroxysmal supraventricular tachycardia[14] without the accompaniment of the rest of the cardiovascular diseases, while in others it appears with familial cardiomyopathy[15]. In 1958, Dausset[16] described the first leucocyte antigen of man. Today 4 locuses of HLA regions are known, and on each there are numerous allelomorphic genes of the codominant characteristics. During these 33 years, antigens of the HLA system have not been published in patients with pre-excitation. Analysis of the antigens of the HLA system in patients with pre-excitation, as a sign of possible connection of the allele of this system with pre-excitation, represents a significant research problem.

The purpose of this study was to analyse the problem of pre-excitation from a clinical-epidemiological and genetic aspects. It was our task to find an answer to the question of how much pre-excitation is present in the general population and whether a connection exists between the antigens of the HLA system and this syndrome in patients with pre-excitation.

Subjects and Methods:

This study is divided into two parts. In the first part data on clinical-epidemiological research on pre-excitation is analyzed. While in the second part antigens of the HLA system are analyzed in patients with various variants of pre-excitation.

During 1969 we examined a population of 4210 healthy subjects in six regions of Croatia: 2049 males and 2161 females, aged from 35 to 54. The subjects were chosen from the population registers of three regions in the interior and three regions at the coast: Zagreb-Centre, Zagreb-Crnomerec, Virovitica, Split-Centre, Vis and Omis: two semi-urban, two urban and two rural regions. Of the total number of those invited, 71% of males and 73.3% of females accepted the examination. The investigation was carried out as part of a study on cardiorespiratory diseases. In each subject an electrocardiogram was performed after a 5 min. rest, with a triple-channel apparatus of the "Cardiolux" type. The following leads were recorded: I-III, aVR-aVF,V_1-V_6. Changes were analysed by means of the Minnesota code[17]. During 1972 all the subjects were again called for an examination of which 83.1% of females and 78.5% of males responded (a total of 80.9%). The examination was repeated in 1982 when 2414 subjects came to be examined, i.e., 57.3% of those from 1969.

Signs of pre-excitation were analysed in the electrocardiogram: P-R(P-Q) interval shorter than 0.12 sec. (code 6-4) and a QRS complex duration of 0.12 sec. or more and duration to the peak of the R wave of 0.06 sec. or more, with simultaneous existence of this finding in the same complexes in any of the leads: I, II, aVL, V_4-V_6 (however with this code types of pre-excitation cannot be differentiated). A short P-R(P-Q) interval was also analyzed (code 6-5): a P-R(P-Q) interval shorter than 0.12 sec. in all complexes in any two of the following leads: I, II, III, aVL, aVF, in the absence of atrioventricular nodal rhythm or sinus tachycardia[17]. The above changes were analysed on three occasions and compared.

In 46 patients from the Division of Cardiology and Outpatient Department, analysis was carried out of HLA system antigens in the Centre for Tissue Typing of the Rebro University Hospital, Zagreb, Croatia. Of these 46 patients, 35 had true WPW syndrome: B type in 26 patients, A type in 6 patients and in 3 patients signs of accessory pathways were present for both the left and the right ventricles. Eleven patients had LGL type of pre-excitation. Antigens of the HLA-locus A, locus B and DR[18] were determined in blood from the peripheral veins by the microlymphocytotoxicity method.

Statistical analysis of obtained parameters was

carried out by testing the difference in the arithmetical means of small independent samples and also the difference in the proportion between the samples[19]. Relative risk was calculated according to Morton and Habel[20]. The presentation was significant if the result was more than 1.

Results

Table 1. shows a finding of pre-excitation according to sex in a general population of 4210 subjects in 1969. A short P-R interval was found in 42 subjects (1.0%). This finding was somewhat more frequent in subjects aged 45 to 49 years. A finding of short P-R interval with widened QRS complex and delta wave was found in two subjects, i.e., 0.05%. One of those subjects had type A and other type B of pre-excitation.

TABLE 1.

PRE-EXCITATION IN THE ELECTROCARDIOGRAM ACCORDING TO AGE IN THE GENERAL POPULATION, 1969 YEAR

Age (Years)	Short P-R interval		Short P-R interval with widened QRS complex and delta wave	
	No.	%	No.	%
35-39 N=1024	13	1.27	1	0.1
40-44 N=1046	5	0.48	0	-
45-49 N=1081	16	1.48	1	0.1
50-54 N=1058	8	0.75	0	-
TOTAL N=4210	42	1.00	2	0.05

Table 2. shows the finding of pre-excitation according to sex. A short P-R interval was rather more frequent in women than in men in a relation 1.06:0.93. A finding of pre-excitation with delta wave was found in two males. These data are from 1969, while in 1982 there were more short P-R intervals: 1.96% in males and 3.22% in females. Two subjects with pre-excitation and delta wave, who had this finding in 1969, failed to report for an examination in 1982.

TABLE 2.

PRE-EXCITATION IN THE ELECTROCARDIOGRAM ACCORDING TO SEX IN THE GENERAL POPULATION DURING A 13-YEAR PERIOD

Sex	Short P-R interval				Short P-R interval with widened QRS complex and delta wave			
	1969		1982		1969		1982	
	No	%	No	%	No	%	No	%
Males 1969 N=2054 1982 N=1326	19	0.93	26	1.96	2	0.10	0	-
Females 1969 N=2161 1982 N=1088	23	1.06	35	3.22	0	-	0	-

Table 3. shows the dynamics of the ECG changes at the time of the two examinations: 1969 and in 1972, and the frequency of the finding in 1982. Of the 42 subjects in whom a short P-R interval was found in the ECG in 1969, only 10 subjects had this finding in 1972 (0.29%). In 22 subjects the finding had disappeared (0.64%), while 10 subjects failed to report for the examination in 1972. This frequency should be treated with reserve, because the number of subjects in the second examination was smaller. Two subjects had a short P-R interval as a new finding in 1972(0.06%). Thus the prevalence of this finding in 1972 amounted to 0.35%. In 1982 the frequency of short P-R interval was higher: 2.53%. In 1969 pre-excitation with delta wave was present in two subjects (0.05%), of these one did not report for examination in 1972. However this finding was found in more subjects in 1972 (intermittent type), so that the prevalence in 1972 amounted to 0.06%.

We determined the HLA system antigen in a group of 46 patients with pre-excitation: 35 with WPW and 11 with LGL syndrome. By microlymphocytotoxicity test we determined antigens of the locuses HLA-A, HLA-B and HLA-DR in all patients. There is no difference in the frequency of certain antigens within the pre-excitation types

TABLE 3.

A FINDING OF PRE-EXCITATION ON THREE OCCASIONS DURING EXAMINATION OF THE SUBJECTS IN A 13-YEAR PERIOD

ECG finding	Total in 1969 N=4210		Has a finding in 1969, and has no finding in 1972		Has a finding in 1969 and in 1972		Has no finding in 1969 and has a finding in 1972		Total 1972 N=3406		Total 1982 N=2414	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Short P-R interval	42	1.00	22	0.65	10	0.29	2	0.06	12	0.35	61	2.53
Short P-R interval with widened QRS complex and delta wave	2	0.05	0	-	1	0.03	-	0.03	2	0.06	0	-

TABLE 4.

THE ANALYSIS OF ANTIGENS OF THE HLA SYSTEM IN PATIENTS WITH PRE-EXCITATION (HLA ANTIGENS OF THE INCREASED FREQUENCY)

HLA antigens	Frequency in the Croatian population %	Frequency in patients with the pre-excitation syndrome %	Statistical significance of the difference (p)	Relative risk
A9	25.14	41.3	0.026	2.1
B5	22.29	41.3	0.0092	2.5
A3	24.57	8.6	0.003	0.28
B14	8.0	0	0.03	0
DR7	18.29	26.19	0.173	1.6

However, we found increased frequency of HLA-A9 antigens (p=0.26) and HLA-B5 (p=0.0092) in the examined group, in comparison with the findings of frequency of the above antigens HLA-A9 and B5 in the Croatian population (N=175). However, the corrected value p for the number of tested antigens of the HLA system is not statistically significant. Data are given in Table 4.

Of the 46 patients, apart from the above HLA-A9 and HLA-B5 antigens, the frequency of the HLA-A3 antigen is significantly less frequent (8.6%) than in the total population (24.57%) while the HLA-B14 antigen was not found in any subject with pre-excitation, and in the total population it amounts to 8.00%. On the other hand, the HLA-DR7 antigen was somewhat more frequently present in patients with the pre-excitation syndrome (26.19%) than in the total population (18.29%). However, the difference is not statistically significant. Of 4 patients with the HLA-DR7 locus, 3 had WPW type of pre-excitation, while LGL was present in only one patient.

Discussion

According to this investigation, a short P-R interval in the ECG is present in 1.0% of the adult population, while a finding of short P-R interval, widened QRS and delta wave is present in 0.05% in cross-section study. These two, however, are difficult to join into one group in this form. Namely, in this populational study a short P-R interval was not constant all the time. In more than half the subjects (22 out of 42) the finding disappeared after three years. In addition, 10 subjects of those with short P-R interval in 1969, did not report for a check-up after three years. This should be taken into account when interpreting the frequency of this finding. The prevalence of this finding after three years was 0.35% only. If one takes into account the possibility that the P-R interval was the same in those subjects who failed to report for the check-up, then it could be concluded that the short P-R interval was counted with the findings in which a widened QRS complex and delta wave exists, a frequency of 0.40% (0.05 and 0.35%). However, even in this way the frequency of this finding cannot be demonstrated, because 13 years after the first examination, a short P-R interval was found in 2.53%. For this reason it is difficult to say what the prevalence is of a short P-R interval in the population because the finding is very variable during the course of time. It should be stressed that on all three occasions of examination during the 13-year period, the ECG findings were always read by the same cardiologyist, coding the changes by the Minnesota code. In these subjects with a short P-R interval in the ECG, it should be an amnestically recorded whether there are any data on paroxysmal tachycardia or tachyarrhythmia in order to assess whether it is a true case of LGL syndrome. In literature[6] the frequency of pre-excitation in a healthy population is reported to be from 0.15%. Our results do not agree with this.

Our two subjects with a short P-R interval, widened QRS complex and delta wave at the beginning of the R wave, one subject did not report for a check-up after three years, while in one subject this finding appeared for the first time. Of these three subjects, type B pre-excitation was present in two and A type in one. B type of pre-excitation is usually reported as being rarer than A type, although according to our clinical data, B type is more frequent than A type, a ratio 2.6:1[10]. In one study[7] of 22,500 workers employed in aviation, pre-excitation was found in as many as 0.25%, which is significantly higher than in Croatian population. However, our study was made in a population selected at random from the population register. We have no find prospective population study in literature dealing the frequency of the pre-excitation.

According to Fisch[21] identical frequency of the pre-excitation syndrome in younger and older people, confirms the assumption of congenital origin of this anomaly. In our investigation the frequency of the HLA-A9 and HLA-B5 locuses in 46 patients with pre-excitation was higher than in a population study in Croatia, while the HLA-A3 locus was significantly rarer in patients with pre-excitation, and the HLA-B14 antigen was not found in any patient, in contrast to a total population of 175 persons. With regard to the HLA locuses, HLA-DR7 was found rather more often in patients with pre-excitation. The difference observed in the frequency of the above locuses of the HLA system antigens between the group of patients with pre-excitation and the control group indicates the possibility of a genetic link between the locuses of the HLA system and predis-

position to this syndrome. However, further research of this link is necessary before a more accurate conclusion can be drawn.

References:

1. Flensted-Jensen R. Wolff-Parkinson-White syndrome- a long term follow-up of 47 cases. Acta Med Scand 1969;186:65-74.
2. Chung RK. Wolff-Parkinson-White syndrome-current views. Am J Med 1977;62:252-266.
3. Ferrer MI. Pre-excitation. Am J Med 1977;62:715-730.
4. Moore EN, Spear JF, Boineau JP. Recent electrophysiologic studies on the Wolff-Parkinson-White syndrome. N Engl J Med 1973;289:956-963.
5. Nicolai P, Medwedovsky JL, Delaahe M, Barnay C, Blache E, Pisapia A. Wolff-Parkinson-White syndrome:T wave abnormalities during normal pathway conduction. J Electrocardiol 1981;14:295-300.
6. Zipes DP. Pre-excitation syndrome, In: Braunwald E ed. Heart disease II edition. WB Saunders. Philadelphia 1984,pp.712-718.
7. Davidoff R, Schamroth CL Myerberg DP. The Wolff-Parkinson-White pattern in healthy air crew. Aviat Space Environ Med 1982;52:544-551.
8. Klein GJ, Hackel DB, Gallagher JJ. Anatomic substrate of impaired antegrade conduction over an accessory atrioventricular pathway in the Wolff-Parkinson-White syndrome. Circulation 1980;61:1249-1250.
9. Anderson RH, Becker AE, Brechenmacher C, Davies MJ, Rossi L. Ventricular preexcitation: a proposed nomenclature for its substrates. Europ J Cardiol 1975;3:27-36.
10. Durakovic Z. Preexcitation. Ann Yugoslav Acad Sci Arts 1988; 436:65-105.
11. Harnischfeger WW. Hereditary occurrence of pre-excitation (Wolff-Parkinson-White) syndrome with re-entry mechanism and concealed conduction. Circulation 1959;19:28-40.
12. Schneider RG. Familial occurrence of Wolff-Parkinson-White syndrome. Am Heart J 1969;78:34-36.
13. Hillmer [illegible] W, Laggaly W. Familienuntersuchungen zum W-P-W syndrom. Z Kreislauff 1971;60:39-99.
14. Gillette PC, Garcon A jr. The pre-excitation syndromes,In: Gillette PC, Garcon A jr eds. Pediatric cardiac dysrhythmias. Grune-Straton. New York 1981.,p.155.
15. Massumi RA. Familial Wolff-Parkinson-White syndrome with cardiomyopathy. Am J Med 1967;43:951-955.
16. Dausset J. Iso-leucoanticorps. Acta Hematol 1958;20:156-160.
17. Rose GA, Blackburn H. Cardiovascular survey methods. WHO Geneva 1968.
18. Terasaki PI, McClleland JD. Microdroplet assay of human serum citotoxins. Nature 1964;204:998-1000.
19. Sachs L. Angewandte statistik. IV ed. Springer Verlag. Berlin 1975,pp.209-216.
20. Morton RF, Habel JR. A study guide to epidemiology and biostatistics. Univ Park Press. Baltimore 1980., pp.1-50.
21. Fisch C. Wolff-Parkinson-White syndrome, In: Braunwald E ed. Heart disease, II edition, WB Saunders. Philadelphia 1984, pp. 220-221.