

A METHOD FOR ESTIMATING INDIVIDUAL PREDISPOSITION TO OCCUPATIONAL FLUOROSIS

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SUMMARY: The occupational fluorosis risk factors were estimated in a three-stage study among the workers of aluminum and cryolite plants using dermatoglyphics as a genetic marker. This study helped: 1) to establish the existence of genetic predisposition to fluorosis and develop criteria for estimating it, and 2) to prove that predisposition to fluorosis was associated with the same dermatoglyphic features in the workers of both industrial groups. Multifactorial analysis of the set of 15 genetic and non-genetic factors was performed with the help of pattern recognition methods, and demonstrated reliable (90-100%) discrimination between two groups of workers: those who had developed fluorosis and those who had not. Each of the 15 risk factors under study was examined for the degree and the direction of influence. A PC software program was developed in the course of the study, making possible the estimation of individual predisposition to the disease. The method was used to investigate 397 disease-free workers in the electrolysis shop of an aluminum plant. Predisposition to fluorosis was discovered in 22 of them (5.5%).

Key words: Occupational fluorosis; Predisposition.

Introduction

Occupational fluorosis presents a serious problem, particularly in the aluminum and cryolite industries. In Russia this disease is estimated to constitute up to 70% of all occupational diseases in these industries.

The main trend in the prevention of occupational fluorosis is maximum possible elimination of fluorine compounds from the working environment. However, this approach has technological limitations, which make important another, additional, approach: to reduce the risk of this disease, even at high fluoride concentrations, by reducing the susceptibility of personnel to it. The latter approach is supported by the fact that the levels of contamination at the existing aluminum and cryolite plants cause fluorosis in a small proportion of workers. The majority of them retire without any marked specific pathology. The above situation suggests an attractive method for detecting particularly fluorosis-susceptible workers or job applicants, which would permit radical improvement of preventive measures.

Materials and Methods

Earlier we developed a methodology to establish criteria for evaluating individual predisposition to occupational diseases (8), and successfully tested it with reference to various pneumoconioses (5,7,8). It seemed reasonable to undertake a similar study for occupational fluorosis. The subjects were selected among the workers of two cryolite and two aluminum plants located in the Urals (Russia).

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In accordance with the methodology, the study was carried out in three successive stages. The first stage consisted of the complex analysis of all the known risk factors. To this end two cohorts were formed from the workers of the cryolite (cohort 1 = 376 workers) and aluminum (cohort 2 = 412 workers) plants who were working in the main production shops on January 1, 1970, and who had no pathological changes characteristic of fluorosis. For each of them we gathered information on 14 basic risk factors for fluorosis (Table 2).

The cohorts were divided into 2 classes: 1) those who did not develop fluorosis: cohort 1 = 245 persons, cohort 2 = 261 persons. 2) those who developed fluorosis: cohort 1 = 131 workers, cohort 2 = 151 workers.

Multifactorial analysis, with the help of the mathematical method of pattern recognition, was aimed at:

- 1) reliably describing the differences between the two classes of workers;
- 2) estimating the degree of influence (informativity) produced by each factor;
- 3) determining the direction of influence for each factor.

The first objective was achieved using the variant of discriminant analysis known as "training by tutor", which consists of selecting at random a sample of 10-12% of observations from the entire set covering both classes for an "exam". The other observations are used to teach the computer, which then will search for relevant discriminating rules. The quality of the rules found is checked by the percentage of correctly recognized observations in the "exam" sample.

The degree of influence (informativity) of each factor was estimated by measuring the Euclidean distance between the centers of the class under consideration. The direction of influence was determined by the rate of occurrence of the factors in these classes.

All of the above problems were solved with the help of the KVAZAR software package (4) developed at the Institute of Mathematics and Mechanics of the Ural Division of the Russian Academy of Sciences.

At the second stage we studied the role of the genotype in the development of fluorosis, using dermatoglyphics as a genetic marker. This choice was determined by our experience of studying genetic predisposition to silicosis, coronary heart diseases and cancer (5,9,10), and literature data on the use of dermatoglyphics for estimating predisposition to endemic fluorosis (1). Our dermatoglyphic methodology, however, was different from the commonly used one.

First of all we had to eliminate the effect of non-genetic factors found to be most influential at the first stage: 4 factors for the cryolite plants (the duration of exposure to fluorine, time of life in the region of fluorine pollution, occupation, and nationality) and 5 for the aluminum plants (occupation, breaks in occupational contact with fluorine, diseases of locomotor system in personal history, alcohol abuse, and nationality) (11,12).

Secondly we analyzed a set of 59 dermatoglyphic features determined for each individual in accordance with the dermatoglyphic nomenclature (6), also using the pattern recognition method mentioned above.

Based on these principles we selected 60 pairs at the cryolite plants and 90 pairs at the aluminum plants matched for the above factors.

At the final third stage we added one more factor, genetic predisposition, to the 14 factors characterizing each individual included in the cohort. Its alternative values ("no" or "yes") were based on estimates obtained at the second stage of the study. Mathematical treatment was carried out in the same sequence as at the first stage.

Results and Discussion

Stage 1

Since the first stage was essentially a preliminary study, and its results have already been published (11,12), we here summarize the most important findings. The best results of pattern recognition in the "exam" sample were obtained in both studies while taking into account all the 14 factors:

Cohort 1

group without fluorosis = 81.4% of correct answers;

group with fluorosis = 66.6%;

Cohort 2

group without fluorosis = 78.2%;

group with fluorosis = 83.3%.

Each of the 14 factors was estimated for its degree and direction of influence.

The results obtained suggest that this set of factors contains sufficient information to provide a satisfactory description of predisposition to fluorosis. To achieve these results, however, we had to use all the selected factors, which confirms the hypothesis that predisposition to fluorosis depends on a multitude of factors. At the same time the impossibility of obtaining better recognition results on the basis of the available information on the risk factors indicates that the set under study lacks some important factors. These missing factors were assumed to be directly related to the genotype.

Stage 2

At this stage we considered the following questions:

- 1) Is there genetic predisposition to occupational fluorosis at all?
- 2) Are there differences in the character of predisposition between the workers of the aluminum and cryolite plants? The second question arose in connection with clinical differences in fluorosis between the workers in these two industries (2).

First we estimated the informativity of each of the 59 dermatoglyphic features. Then all the available information about these features was considered for sufficiency for describing differences in the dermatoglyphic picture of those who had developed fluorosis and those who had not. For the cryolite plant reliable discriminating rules (83% of correct recognitions at the "exam") were obtained using 7-10 most informative features (Table 1) (11).

For the aluminum plants the best results (100% correct answers) were obtained with 10 dermatoglyphic features taken into account.

Table 1. Most informative dermatoglyphic features

No.	Name of feature
1	Width of palm lines on right hand
2	Direction of main palm line D on left hand
3	Ball pattern of finger 1 of right hand
4	Palm ridge count ab of right hand
5	Ball pattern of finger IV of right hand
6	Pattern in zone between fingers IV and V of left hand
7	Palm ridge count cd of left hand
8	Ball pattern of finger I of left hand
9	Direction of main palm line B on left hand
10	Palm ridge count ab on left hand

The direction of influence of each of these features was also found to match in both cohorts. The possibility of obtaining reliable discriminating rules using subsets of 7-10 features only (out of 59) points to significant differences in the dermatoglyphic pattern between workers who had developed occupational fluorosis and those who had not.

Agreement between the results obtained for the workers of the industries under consideration permitted us to discard the hypothesis that there are differences in the nature of genetic predisposition to fluorosis between the workers of the aluminum and cryolite plants. As regards clinical differences between the "cryolite" and "aluminum" fluoroses reported in the literature, this fact may be explained by the action of other "non-fluoride" industrial factors which are different for these industries.

Stage 3

At the final stage we examined each member of the experimental cohorts for the presence or absence of genetic predisposition to fluorosis using the best discriminating rules. Each subject was thus characterized by a set of 15 genetic and non-genetic factors.

First we determined the degree of influence produced by each of these factors. Table 2 shows that the phenotype of predisposition to fluorosis ranks first in both studies. Thus, the contribution of the genetic component is sufficiently high even against the action of many other factors. The features characterizing fluorine exposure rank high as well.

Next we checked whether the information on the above 15 risk factors was sufficient for ensuring the discrimination between patterns of predisposition and non-predisposition to fluorosis. Best recognition of the "exam" patterns was achieved using 14 most informative features for cohort 1 (100% correct answers for both groups) and 13 features for cohort 2 (93.75% of correct answers for those who had not developed fluorosis and 100% for the cases of fluorosis).

Comparison of these results with those obtained at stage 1 demonstrates that the inclusion of information on genetic predisposition ensured higher problem-solving reliability.

Examination of each feature for the nature of its influence clearly demonstrated that in both industries genetically predisposed individuals (as detected dermatoglyphically) are more likely to develop fluorosis.

Predisposition to fluorosis does not mean, however, that this disease is unavoidable. Its selective development in different individuals depends on a particular combination (favorable or unfavorable) of genetic and non-genetic factors. The effect of the group of features characterizing fluorine exposure is very important as well.

Table 2. Significance of various factors for development of fluorosis in workers of cryolite and aluminum industries

Factor	Aluminum		Cryolite	
	Rank	Informativity	Rank	Informativity
Genetic predisposition	1	1.00	1	1.00
Personal small-holding	2	0.654	5	0.251
Duration of living in fluorine-contaminated area before occupational exposure	3	0.584	4	0.256
Duration of occupational exposure to fluorine	4	0.482	2	0.643
Occupation	5	0.316	6	0.123
Smoking	6	0.158	13	0.016
Nationality	7	0.139	10	0.069
Diseases of locomotor system in personal history	8	0.102	9	0.077
Availability of modern housing conditions	9	0.102	3	0.593
Alcohol abuse	10	0.086	12	0.024
Diseases of liver in personal history	11	0.082	15	0.001
Diseases of kidneys in personal history	12	0.055	14	0.004
Breaks in occupational exposure to fluorine	13	0.023	7	0.115
Diseases of endocrine system in personal history	14	0.006	11	0.053
Age at beginning of occupational exposure to fluorine	15	0.002	8	0.098

Analysis of the factor "duration of occupational exposure to fluorine" for the direction of its influence demonstrates a two-phase character of dependence. The risk of fluorosis grows throughout the initial period of exposure from 1 to 15 years, going down afterwards. This can be explained by the accumulation of fluorine in the organism, which increases the probability of developing this disease. During the second phase the most susceptible individuals have to leave the industry, and the remaining workers stay healthy, exhibiting greater resistance despite the continuing exposure, which accounts for the decrease in the risk of developing fluorosis.

The duration of living in a fluorine-contaminated area was observed to have a direct effect on the development of fluorosis, which may be attributed to the exposure to additional fluorine.

All the workers of the cryolite plants were divided professionally into two groups: 1) those working in direct contact with both hydrogen fluoride (HF) and fluorine salts; 2) those exposed predominantly to HF. The first group exhibited a higher probability of developing fluorosis due to their higher exposure to fluorine, and due to the specific toxicokinetic properties of gaseous and aerosol fluorine compounds that are responsible for their retention in the organism.

All the workers in the electrolysis shops at the aluminum plants were divided into three groups: 1) auxiliary personnel; 2) anode workers; and 3) electrolyzers. The risk of fluorosis was found to be highest for the third group and lowest for the first group.

Breaks in the exposure to fluorine reduces the risk of fluorosis, which is in agreement with the findings of other researchers (3).

Social factors contribute greatly to individual predisposition to fluorosis. Thus, smoking, alcohol abuse, unsatisfactory housing conditions and the availability of a personal small-holding increase the risk of fluorosis as the direction of their influence demonstrates it. As regards the last factor in the above list of social factors, we think that its negative role may be explained by additional intake of fluorine compounds from vegetables grown on small holdings located within fluorine-contaminated areas.

Biological factors were found to make an additional contribution to the predisposition to fluorosis. Thus, first occupational exposure at the age of 18-26 accounts for a higher risk of fluorosis than that at the age of 30-40. Young people demonstrate greater susceptibility to toxic effects of fluorine compounds, which is likely to be due to functional immaturity of their protective mechanisms.

Of the two basic ethnic groups inhabiting the Ural region - Russians and Turks - the former demonstrate higher susceptibility to fluorosis.

Thus, studies carried out in two fluorosis-hazardous industries show good agreement as regards the effect of genetic and non-genetic risk factors. This fact proves that the methodology used was adequate to the problem under study.

The discriminating rules elaborated at stages 2 and 3 may be used for detecting fluorosis-susceptible individuals among both employees and applicants.

At the end of 1993 we used this method at one of the aluminum plants to investigate 397 electrolysis workers who did not exhibit any signs of fluorine

intoxication at the time of examination. Of these, 22 workers (5.5%) demonstrated higher individual susceptibility. We are planning to investigate all the workers (about 2000) employed in the electrolysis shops of this plant. A follow-up study of this group will permit us to estimate the actual accuracy of this method in the estimation of individual predisposition to fluorosis.

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