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ARTICLES

A POSSIBLE GENETIC FACTOR IN THE ETIOLOGY OF PORPHYRIA TURCICA

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Students of metabolic disturbances have been greatly interested in the outbreak of a new type of cutaneous porphyria in southeastern Turkey in, and since, 1955. No similar syndrome had been previously reported and the nature of the disease was so striking that it was readily accepted as a «new» disease. This fact alone was enough, in the minds of many observers, to rule out any hereditary or genetic factors as contributory to this type of porphyria. The unequivocal role of hexachlorobenzene as a causative agent was clearly demonstrated and was accepted as further proof of the absence of any genetic factor in the etiology of the disease. Additional evidence for this point of view was drawn from the nature of the local population, which consists of old Turkish settlers, immigrant Turks and Kurds. It was claimed that, since the disease occurred with equal frequency in these three «genetically distinct» populations, it could obviously not have a genetic background.[1]

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As Schmid[2] and Watson[3] have both pointed out, if the foregoing arguments are valid, this disease must be described as the first example of an acquired porphyria in man arising without regard to genetic or constitutional factors. This assumption was of sufficient importance to have led some authors to revise the classification of porphyrias.[2,3]

During our study of the Turkish type of cutaneous porphyria, undertaken in the summer of 1958, and especially in our field studies and surveys in southeastern Turkey the following observations were made:

1. Exposure of the local population to hexachlorobenzene was virtually complete in some areas but the incidence of porphyria was very small. Explanation of the exposure to hexachlorobenzene is as follows : In the fall of 1954, seed wheat shipments into certain villages and townships in the region were delayed and the farmers were forced to buy up the local supplies of wheat to plant. When the seed wheat (treated with hexachlorobenzene) finally arrived, it replaced the wheat which had been planted and was consumed more or less equally by virtually all the inhabitants.

Despite this widespread exposure, only a small fraction of the population developed porphyria. In the town of Bismil, for example, where the percentage of affected individuals was one of the highest in the region, less than 150 people out of a total population of 3,000 (almost all of whom were known to have eaten treated wheat) were affected.

2. Frequently more than one member of a family was affected in families with porphyria.

3. In several families where one man had married twice it was found that all the children of one mother were affected while the children of the other mother escaped, although all had eaten treated wheat.

4. In some instances where two families shared a house and prepared food (including baking bread) in common it was found that the children of only one of the families were affected.

5. In the year 1958, when hexachlorobenzene ingestion had been established as the direct cause of porphyria, some villagers continued to deny that this could be so since they claimed to have eaten the treated wheat for at least a year with no ill effect. As a matter

of fact it was this situation which delayed the pinpointing of hexachlorobenzene as the causative agent for some two years.

The Genetic Basis of Predisposition to Porphyria

In view of these observations we feel warranted to consider the possibility that some sort of constitutional predisposition exists, which permits hexachlorobenzene to be effective in precipitating porphyria, and that a genetic factor is the most likely possibility. Arguments against this position can be rebutted as follows :

a) The fact that the disease had not been seen in the past is not enough to rule out genetic predisposition since the population had not been previously exposed to hexachlorobenzene. Since it has been demonstrated that this exposure is the immediate cause of the disease, in the absence of such exposure it cannot be determined whether or not a hereditary predisposition to porphyria existed in the ancestors of the present population. However it does not seem illogical to assume that such a predisposition existed and passed benignly from generation to generation until such time as the disease was triggered in susceptible individuals by hexachlorobenzene exposure.

b) The fact that the disease occurs with equal frequency in Turks, Kurds and Turkish immigrants cannot be accepted as an argument against genetic predisposition since even strictly isolated populations with distinct origins cannot be regarded as having entirely unique genotypes. Such populations may differ from others in respect to the frequencies of certain genes but it is hard to believe that the three populations of southeastern Turkey would originally have developed different frequencies of the genes which might cause variability in predisposition to porphyria since the environmental conditions for the expression of these genes were absent at the time that the populations were separated. That is, such genes would have had no selective advantages or disadvantages in any of these populations and hence it is quite unlikely that any significant difference from normal frequencies would have arisen in any one of the three populations. Moreover, intermarriage among the people of these three groups has been quite common and it is probable that a new level of genetic equilibrium has been established in the population at large as a result of interbreeding.

Dominance of the Gene

In affected families, the disease is not usually seen in the parents despite their common exposure to hexachlorobenzene. Here there are two possibilities : a) either the gene is recessive, or b) the gene may be dominant but of low penetrance in older age groups. Let us examine these possibilities one by one :

In the families of 376 affected individuals, who were recently restudied, it was determined that in no instance were both parents affected. In a group with the rate of incidence found in southeastern Turkey, it would be expected that in some families both parents would be homozygous and would thus manifest the disease if it were due to a recessive gene. There is, moreover, reason to believe that the postulated dominant gene has very low penetrance in older persons. Table 1 shows that incidence varies with age in both sexes. While 64.6 per cent of the 6-10 year old males in the study were

TABLE 1

INCIDENCE OF PORPHYRIA IN THE MALE AND FEMALE OFFSPRING OF PARENTS WITH AT LEAST ONE AFFECTED CHILD

	MALES				FEMALES				
Age	Diseased	Normal	Total	Per Cent Diseased	Diseased	Normal	Total	Per Cent Diseased	Total of all children
0—5	42	55	97	43.3	29	44	73	39.7	170
6—10	146	80	226	64.6	74	65	139	53.2	365
11—15	35	95	130	26.9	19	76	95	20.0	225
16—	22	120	142	15.5	9	84	93	9.7	235
Total	245	350	595		131	269	400		995

affected, the relative incidence in males of 16 years and above was only 15.5 per cent. Incidence in adults beyond 25 years of age was about 1 per cent.

Statistical Control

Some serious difficulties arise in connection with the statistical control of the hypothesis that a single dominant gene is responsible for predisposition to this type of porphyria. These difficulties relate to the facts that the parents cannot be classified phenotypically due to the low penetrance of the gene; that the disease is largely confined to one generation; and that the rate of incidence varies from age

TABLE 2

INCIDENCE OF PORPHYRIA IN THE OFFSPRING OF PARENTS WITH AT LEAST ONE AFFECTED CHILD WITHOUT REGARD TO SEX
(combined data from table 1)

Age groups	Affected	Normal	Total	Per Cent Affected
0—5	71	99	170	41.8
6—10	220	145	365	60.3
11—15	54	171	225	24.0
16—	31	204	235	13.2

TABLE 3

THE GENOTYPES OF THE PARENTS OF AFFECTED CHILDREN AND THE RELATIVE FREQUENCIES OF EACH TYPE OF MATING AND OF OFFSPRING RESULTING FROM THESE MATINGS.

Matings	Frequency of Matings	Frequency of Offspring	
		Affected	Normal
TTxTT	p^2p^2	p^4	—
TtxTT	$2\ pq.p^2$	$2\ p^3q$	—
TTxTt	$p^2.\ 2\ pq$	$2\ p^3q$	—
TtxTt	$2\ pq.\ 2\ pq$	$3\ p^2\ q^2$	$p^2\ q^2$
TTxtt	$p^2.\ q^2$	$p^2\ q^2$	—
ttxTT	$q^2.\ p^2$	$p^2\ q^2$	—
Ttxtt	$2\ pq\ q^2$	pq^3	pq^3
ttxTt	$q^2.\ 2\ pq$	pq^3	pq^3

Ratio of normal offspring to all:

$$\frac{p^2q^2 + 2pq^3}{p^4 + 4p^3q + 6p^2q^2 + 4pq^3} = 0.447 \quad \text{when } q = 0.9 \text{ and } p = 0.1$$

(p equals the frequency of the gene, T, which causes the predisposition to porphyria, and q equals the frequency of its allele, t, the normal gene which does not cause predisposition to porphyria) 5.

group to age group. However, the rules of population genetics supply some convincing evidence for the hypothesis :

The figures in tables 1 and 2 were obtained from families with at least one affected child. According to the hypothesis, these families were of the genotypes shown in table 3. The same table also includes the theoretical frequencies of different types of mating and of offspring. The expected frequency of normal children, compared to the frequency of all children, is given beneath the table. If q (the frequency of the recessive gene) is known, this ratio can be solved easily to give us the expected number of normal children in the families described. Because of the low penetrance of the gene in question, it is highly difficult to estimate the value for q. If the penetrance of the gene T was 100 per cent, all the normal children would have been of the genotype tt. In this case, however, there must also be some T-carrying normal children. The penetrance of T was assumed to be complete in the children of 6-10 years of age since the incidence

TABLE 4

CHI-SQUARE TEST FOR FITNESS OF THE EXPECTED TO THE ACTUAL NUMBERS OF NORMAL AND AFFECTED CHILDREN IN THE 6-10 YEAR AGE GROUP.

	Observed* (×)	Expected** (m)	$\frac{(\times - m)^2}{m}$
Normal	145	163	1.988
Affected	220	202	1.604
Total	365	365	$x^2 = 2.592$***

of porphyria was highest in that age group. From observations in certain communities, such as Bismil, it was estimated that 81 per cent of the 6-10 year old children were normal, that is of the genotype tt. This can be taken as the value for q^2 according to the Hardy - Weinberg law. Thus q equals the square root of 0.81 or 0.9. Using this value for q in the ratio given under table 3, we come out with a figure of 0.447 (or 44.7 per cent). This is the expected per cent of normal children to be found in affected families if the hypothesis is valid and gives us a figure of 163 children out of 365. In table 2 the actual number of normal 6-10 year old children was given as 145. The discrepancy between the expected hypothetical figure and the actual one

* From Table 2
** $365 \times 0.447 = 163$; $365 - 163 = 202$.
*** 0.20 P 0.10

is not statistically significant as is demonstrated by chi-square test in table 4. This constitutes statistical evidence for the validity of the hypothesis.

Conclusion

Until more convincing evidence for another hypothesis is provided, it seems permissible to accept the hypothesis that genetic predisposition to a type of porphyria does exist in southeastern Turkey and that it is transmitted by a single dominant gene of variable penetrance in different age groups.

Summary

Evidence for the existence of a genetic factor in the etiology of porphyria turcica is presented together with a statistical analysis of the probable genetic situation in families with affected children.

The comparatively low incidence of the disease in areas where virtually the entire population is known to have been exposed to hexachlorobenzene, the precipitating agent, together with the facts that affected families frequently included more than one member with porphyria and that in several families containing half brothers and sisters the children of one mother escaped while those of the other were affected, are all cited as reasons for concluding that a predisposing factor must exist side by side with the causative, or triggering, factor of hexachlorobenzene ingestion. The nature of the outbreak is such that the historically diverse origins of the local population do not preclude genetic predisposition and are felt to be of comparatively little significance, particularly in view of the large amount of intermarriage and the consequent mingling of genes that has taken place in the region.

Evidence from field studies that this disease practically never appears in both parents in affected families despite their common exposure to hexachlorobenzene, indicating a recessive gene, combined with evidence that this form of porphyria is largely confined to children and adolescents, is presented as support for the hypothesis that there is, indeed, a genetic factor involved in porphyria turcica and that in all probability the defect is transmitted by a dominant gene of low penetrance in older persons.

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