PORPHYRIA TURCICA

A Survey of 592 Cases of Cutaneous Porphyria Seen in Southeastern Turkey

Ihsan Doğramacı, M.D.,* Joe D. Wray, M.D.,**
Turhan Ergene, M.D.,*** **Vedat Sezer, M.D.,****
and Yunus Müftü, M.D.***

References to the outbreak of the cutaneous type of porphyria which began to occur in southeastern Turkey in the summer of 1955 have been made by various authors. [1-9]

It seemed from the very start that certain aspects of the disease could best be studied in the field, using a survey approach. The data to be reported in this present paper have been collected in the course of a field survey carried out in the Diyarbakir region. The first part of the survey was conducted by Dr. Vedat Sezer, over a three month period from December 1958 through February 1959, and the second part by Dr. Turhan Ergene during May and June of 1960.

The combined information from the two parts of the survey provides an understanding of many of the important features of the outbreak.

Basic Plan of the Survey

The survey was planned to provide as much information as possible about the following aspects of the outbreak :

1. The basic clinical pattern of the disease as observed in a large number of patients with regard both to individual histories and to physical findings.

From the Department of Pediatrics of Ankara University Hacettepe Medical Center and Hacettepe Children's Hospital.
* Professor of Pediatrics and Chairman of the Department.
** Associate in Pediatrics.
*** Assistant in Pediatrics.
This investigation was supported in part by research grant A-4436 from the National Institutes of Health, Public Health Service, USA.

2. Basic data from normal or non - affected children especially in regard to their nutritional state judged by height and weight measurements.

3. The epidemiologic pattern of the disease and etiologic factors involved in its development. The results in regard to etiology have been reported elsewhere.[10]

Method and Case Material

It was felt that a convenient way to approach the problem in the field was simply to visit towns and villages in the region and to interview and examine as many individuals suffering from the disease as possible. With this in mind a mimeographed form was prepared for use as a guide in the interview and for recording the findings, both at interview and on physical examination. It was considered essential to keep the questions as simple and objective as possible, seeking only information that seemed likely to contribute significantly to the study. Similarly, prior acquaintance with the disease made it possible for us to single out for examination those physical features which seemed likely to contribute to our understanding.

Although it was considered unlikely that every patient with the disease could be found and examined, the investigators were determined to find as many as possible. In the second part of the survey a determined effort was made to locate individuals not found in the first part. Using this approach 592 individuals residing in 30 towns and villages were found and included in the survey. The field investigator himself interviewed and examined all patients, and usually recorded the data, as well. Although it was impossible for V. S. to conduct the second part of the survey, an attempt was made to reduce differences attributable to the different investigators by providing an opportunity for V. S. to orient T. E. in the field. This orientation included instruction in the supervision of the interviews, the conducting of examinations and the taking of records and occupied several days at the start of the second part of the survey. Interpretation of patients' histories and physical findings was thus similar in both parts of the survey.

Age and sex incidence

Of 592 patients 381 were males and 211 females. Table 1 summarizes these findings in five - year age groups and emphasizes the peak incidence in the 6 to 10 year age group in both sexes, followed by the 11 to 15 year group.

TABLE 1

AGE AND SEX INCIDENCE OF PORPHYRIA TURCICA

Age group	Males	Females	Total
Under 5	20	15	35
6—10	188	115	303
11—15	122	67	189
16—20	16	4	20
Over 20	35	10	45
Total	381	211	592

These figures suggest a strong preponderance of males over females in all age groups. However, the actual situation is revealed in another study.[11] Here, a consideration of the total unaffected child population of 619 individuals (350 males and 269 females) living under the same conditions as, and mostly siblings of, 376 affected individuals (245 males and 131 females), showed that the total number of males was greater than the total number of females in each age group, indicating that there is no significant difference in susceptibility between males and females.

General Nutritional Status

It was hoped that study of the height - weight data of the patients, in comparison with non - affected age - peer controls from the same region, would provide at least a reliable clue to the general nutritional status of the children involved.

In seeking data from non - affected children the largest possible sample was desired. This was achieved by using the «cluster sample» technique; schools were visited throughout the region and all available children were weighed, measured and examined briefly to determine the incidence of liver enlargement and arthritic changes. Over 3,000 children living in the region were examined in this fashion, providing us with ample data on both males and females between the ages of 7 and 13, inclusive. In all cases the investigator himself examined the children. The school teacher was usually enlisted to record the findings on the prepared form. The findings are listed in tables 2 - 5.

It is clear from these figures that children afflicted with the disease were significantly shorter and weighed less than their age peers in the region. It was difficult to decide conclusively whether the disease appeared more frequently in children who were less

TABLE 2

MEAN BODY HEIGHT OF MALES (IN CENTIMETERS)

Age	Controls	Patients
6		104.5
7 *	116.44	110.7
8 *	121.42	116.3
9 *	125.44	120.7
10 *	129.12	124.5
11 *	133.12	128.6
12 **	137.40	134.7
13 *	141.44	136.7
14		144.7

* Difference between controls and patients statistically significant.
** Difference between controls and patients not statistically significant.

TABLE 3

MEAN BODY WEIGHT OF MALES (IN KILOGRAMS)

Age	Controls	Patients
6		16.04
7 *	21.68.	18.48
8 *	23.74	21.02
9 *	25.60	22.55
10 *	27.42	23.87
11 *	29.45	27.02
12 *	31.65	29.14
13 *	34.25	30.82
14		34.18

* Difference between controls and patients statistically significant.

well - developed and less well - nourished than other children, or whether at the time of examination of these children their growth had slowed as a result of the disease. Since the average duration of illness at the time of examination was about two years it was our feeling that the latter assumption was probably better founded.

TABLE 4
MEAN BODY HEIGHT OF FEMALES (IN CENTIMETERS)

Age	Controls	Patients
6		101.7
7 *	114.74	109.9
8 *	120.16	113.6
9 *	124.96	117.2
10 **	125.11	124.4
11 **	132.38	128.4
12 *	138.04	129.4
13 **	141.94	136.8
14		145.2

* Difference between controls and patients statistically significant.
** Difference between controls and patients not statistically significant.

TABLE 5
MEAN BODY WEIGHT OF FEMALES (IN KILOGRAMS)

Age	Controls	Patients
6		14.69
7 *	20.17	17.42
8 *	22.67	19.46
9 *	24.69	21.32
10 **	25.49	23.46
11 *	28.91	25.30
12 *	32.36	26.68
13 *	34.15	28.65
14		36.04

* Difference between controls and patients statistically significant.
** Difference between controls and patients not statistically significant.

Order of Signs or Symptoms

One of our first concerns was to try to gain an understanding of the pattern of onset of the disease. Patients interviewed were therefore asked to specify the order in which various signs or symptoms appeared. Table 6 summarizes the findings thus obtained. Weakness, occasionally associated with loss of appetite, cutaneous photosensitivity, and porphyrinuria, per se, were the most common

presenting features and these eventually developed in the overwhelming majority of the patients. Hypertrichosis and hyperpigmentation were the next most common symptoms and these two developed eventually in most patients. There were occasional complaints of itching at the onset and a few individuals reported friability of the skin. Fever was also occasionally reported but this was almost certainly due to intercurrent infection.

It is evident from table 6 that there was no set pattern for the development of the signs and symptoms which characterized the disease in these patients. Neither was the time factor predictable. Because of the limitations noted, detailed information was not sought, but interviews with reliable patients indicated that onset was gradual, extending over a period of several weeks, and was likely to be most rapid in those patients in which the illness first appeared in the late spring or summer.

Because of the notable occurrence of neurological symptoms and severe abdominal pain and/or colic in patients with acute intermittent porphyria (A. I. P.), these symptoms were given special attention in the survey. Neurological symptoms of any kind simply were not reported. Abdominal pain, on the other hand, was mentioned as a presenting symptom by 13.5 per cent of the males and 31.4 per cent of the females, and was present at some time during the illness in over one half of the patients. In no case, however, had there been pain of the degree of severity characteristic of A. I. P and not one of these patients had been subjected to an exploratory laparotomy as so frequently happens to patients with A. I. P.

The disease had been present in the patients interviewed for an average of approximately two years. All patients reported seasonal variations in the course of the disease, the skin lesions being relatively quiescent during the winter. Variations in hypertrichosis and hyperpigmentation were not remarkable.

Physical Findings

General Condition. The general condition of the patients examined was good. Though «weakness» was a common complaint, the disease is by no means totally debilitating and, in general, victims were quite capable of pursuing their normal activities. Two significant problems were prevalent, however, the first of them being the degree of hypertrichosis present in many of the girls. The emotional effect of this disfiguring phenomenon was perhaps lessened some-

TABLE 6

ORDER OF APPEARANCE OF SIGNS AND SYMPTOMS IN 3-20 YEAR OLDS*

Symptoms	Weakness	Bullae	Red Urine	Hypertrichosis	Pigmentation
No. of males					
First Symptom	135	101	63	36	15
Second »	115	105	84	81	28
Third »	63	82	107	100	58
Fourth »	11	56	67	66	140
Total	324(93.6%)	344 (99.4%)	321 (92.8%)	283(81.8%)	241(69.7%)
No. of Females					
First Symptom	86	43	61	22	5
Second »	67	53	39	73	22
Third »	34	65	65	43	26
Fourth »	7	40	36	29	61
Total	194(96.5%)	201(100.0%)	201(100.0%)	167(83.08%)	114(56.7%)
GRAND TOTAL	518(94.7%)	545 (99.6%)	522 (95.4%)	450(82.3%)	355(64.9%)

* 45 patients above 20 years of age are not included.

what by its prevalence in the region, but it constituted a serious problem for many girls. The other notable problem was due to complications arising out of secondary infection of the bullae which were, in turn, the result of the cutaneous photosensitivity. The bullae, frequently one centimeter or more in diameter and quite tense, inevitably ruptured leaving an area exceedingly susceptible to local infection. Such infection delayed healing and increased the amount of scarring, frequently producing regional lymphadenitis.

Vital Signs. Pulse and blood pressure were measured and were within the normal range in all cases. Fever was not a feature of the disease in the absence of secondary infection.

The outstanding physical findings in the disease are the changes produced by the photosensitivity and their sequelae. These changes were subject to considerable seasonal variation, but practically one hundred per cent of the patients reported their presence at some time during the course of their illness. They occurred only on areas exposed to sunlight, primarily the face and distal extremities. In the field survey lesions were actually observed in 92 percent of the males and 94 per cent of the females examined. The lesions were graded as mild, moderate or severe depending on severity and extent. Patients with lesions classified as mild had occasional or scattered bullae or their scars. Those whose affliction was classified as moderate had numerous such lesions on exposed areas and those with severe involvement had lesions, either recent or old, almost completely covering the exposed areas. Excessive pigmentation was not considered separately in the survey since it uniformly occurred in the scars of the healed bullae and its incidence parallels that of other skin changes. Hypertrichosis was evident in a large majority of the patients examined (see fig. 1). As can be seen from table 6, it eventually appeared in 450 out of 547 patients (45 patients over 20 years of age were excluded from this tabulation).

Liver enlargement was present in 33 per cent of the patients and the liver was found to be tender in approximately one third of porphyric patients. Enlargement tended to be more common in the younger age groups but tenderness was more frequently found in the older age groups. Liver condition in this disease has been reported previously by Doğramacı and co-workers.[12]

«Rheumatoid» arthritic changes were observed in 214 out of 592 patients (36.1 per cent) in the present survey. A further inves-

tigation of the patients affected with porphyria turcica, two and a half years after the present survey, showed that the incidence of arthritis had increased to 54.8 per cent in 376 cases, whereas most of the other symptoms of the acute disease, including porphyrinuria had subsided.[13] Since this remarkable finding has apparently

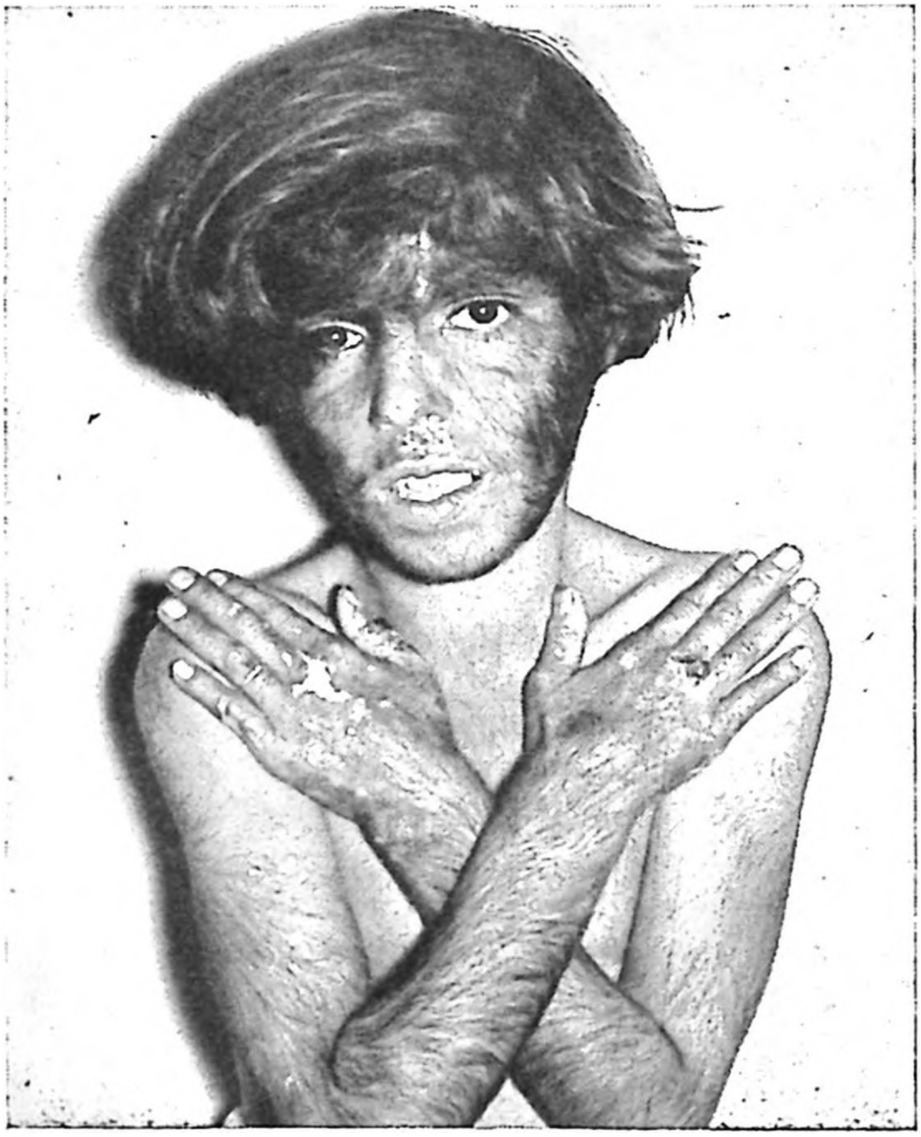

Fig. 1. V.C., 13 year old female
Showing hypertrichosis, hyperpigmentation, and bullae.

not been previously associated with any known form of porphyria, there remained, in spite of the high incidence, the possibility of coincidence. The survey of the school children in the region, however, revealed not one child with similar changes; adequate evidence that arthritis is a feature of the disease under study.

Enlargement of the thyroid gland was another feature in a large number of the patients. Since goiter is endemic in this region, a survey is currently being made to establish the incidence of thyroid

enlargement in the general population in this area. The results will be the subject of another report.

Summary

A comprehensive report of a field survey, covering 592 cases of porphyria turcica, the cutaneous porphyria seen in southeastern Turkey, is presented.

The basic plan of the survey is described and the results with regard to presenting signs and symptoms and the epidemiologic pattern of the disease are set forth in the text and in tabular form. The evidence uncovered in the survey is weighed against information derived from a group of over 3,000 nonaffected children living in the same region, especially in regard to nutritional status as judged by weight and height measurements.

It is concluded that weakness, cutaneous photosensitivity and porphyrinuria are the most common presenting features of the disease, followed by hypertrichosis and hyperpigmentation which are eventually manifested by the majority of patients. Neurologic symptoms do not seem to be a feature of this form of porphyria but abdominal pain was reported in some cases and liver enlargement was found to be present in 33 per cent of the cases surveyed. The remarkable finding of arthritic changes in 36.1 per cent of the patients in the early stages of the disease is reported, together with the later finding that the incidence of arthritic changes had risen to 54.8 per cent at the end of another two and a half year interval during which time other signs diminished.

The peak incidence of the disease was found to be in the 6 to 10 year age group, followed by the 11 to 15 year group. Sex differences were not found to be significant. All patients reported seasonal fluctuations in the course of the disease.

REFERENCES

1. Çam C.: Dört porphyrie congénitale vak'ası, Neşter **1**: 2, 1957.
2. Soysal, S. S., Bilger, M., and Neyzi, O.: A propos de deux cas de porphyrie du type «Cutanea tarda,» Arch. Franc. Pediat. **16**: 1084, 1959.
3. Çam, C.: Intoksikasyona bağlı deri porfirileri, Dirim **34**: 11, 1959.
4. Doğramacı, İ.: Porphyria, Annales de l'Universite d'Ankara **7**: 1, 1959.
5. Çam, C.: Toxic and acquired cutaneous porphyrias caused by hexachlorobenzene, Bull. Soc. Med. Hop. Paris **76**: 1305, 1960.

6. Çetingil, A. I., and Özen, M. A.: Toxic porphyria, Blood 16: 1002, 1960.

7. Schmid, R.: Cutaneous porphyria in Turkey, New England J. Med. 263: 397, 1960.

8. Doğramacı, İ: An outbreak of toxic porphyria in southeastern Turkey (editorial), Turkish J. Ped. 3: 57, 1961.

9. Dean, G.: The Turkish epidemic of porphyria, South African M. J. 35: 509, 1961.

10. Wray, J. D., Müftü, Y., and Doğramacı, İ.: Hexachlorobenzene as a cause of porphyria turcica, Turkish J. Ped. 4: 132, 1962.

11. Doğramacı, İ., Ergene, T., and Göçmen A.: Age and sex in porphyria turcica (to be reported).

12. Doğramacı, İ., Tınaztepe, B., and Günalp, A.: Condition of the liver in patients with toxic cutaneous porphyria, Turkish J. Ped. 4: 103, 1962.

13. Doğramacı, İ., Kenanoğlu, A., Müftü. Y., Ergene, T., and Wray. J. D.: Bone and joint changes in patients with porphyria turcica, Turkish J. Ped. 4: 149, 1962.