

L-xylulosuria in a Lebanese Family

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L-XYLULOSURIA (PENTOSURIA) is an inborn error of metabolism characterized by the presence in the urine of the ketopentose *L*-xylulose (synonyms: *L*-xyloketose, *L*-threo-pentulose, *L*-threo-ketopentose; Pigman, 1957). It is a harmless condition and no treatment is required. It is also an extremely rare condition and altogether only about 200 cases have been described in the literature (Knox, 1958; Touster, 1959). Most of these cases have occurred in small family groups with a familial incidence. Our investigation is of a large kindred, embracing four generations of a Lebanese family. The occurrence of *L*-xylulosuria in two sisters of this family (Fig. 1: V-16 and V-19) was previously reported by Barnes and Bloomberg (1953).

SUBJECTS

The investigation was carried out on 127 members of a Lebanese kindred (103 in direct line of descent through four generations and 24 absorbed by marriage into the family), living in Johannesburg. Their ages varied from a few days to 95 years of age. Their relationships to each other are shown in the pedigree (Fig. 1). Among direct descendents there were 48 males and 55 females, and in the entire kindred 59 males and 68 females. Nine infants were born while the investigation was in progress, and other infants who died early in life were not included in this study. Only those subjects who have been examined in this investigation have been included in the pedigree. Bisected symbols refer to dead ancestors and have being included only to indicate family relationships.

Two sisters (III-2 and III-4) of the third generation emigrated with their husbands to South Africa in 1902 from Sibhil, a small village in Lebanon. Two close intermarriages can be traced, namely between IV-8 and IV-9 who are first cousins, and between III-5 and IV-18 who are first cousins once removed. No consanguinity could be established for the remaining spouses who, in fact, came from different parts of Lebanon.

METHODS

This investigation was carried out over a period of four years. As it proved impractical to obtain 24 hour specimens of urine, early morning specimens only were collected periodically from each subject during the four year period of this investigation. No preservative was added. Within one hour of collection the urines were placed into the refrigerator, and all tests were commenced within 24 hours. The following tests were carried out:

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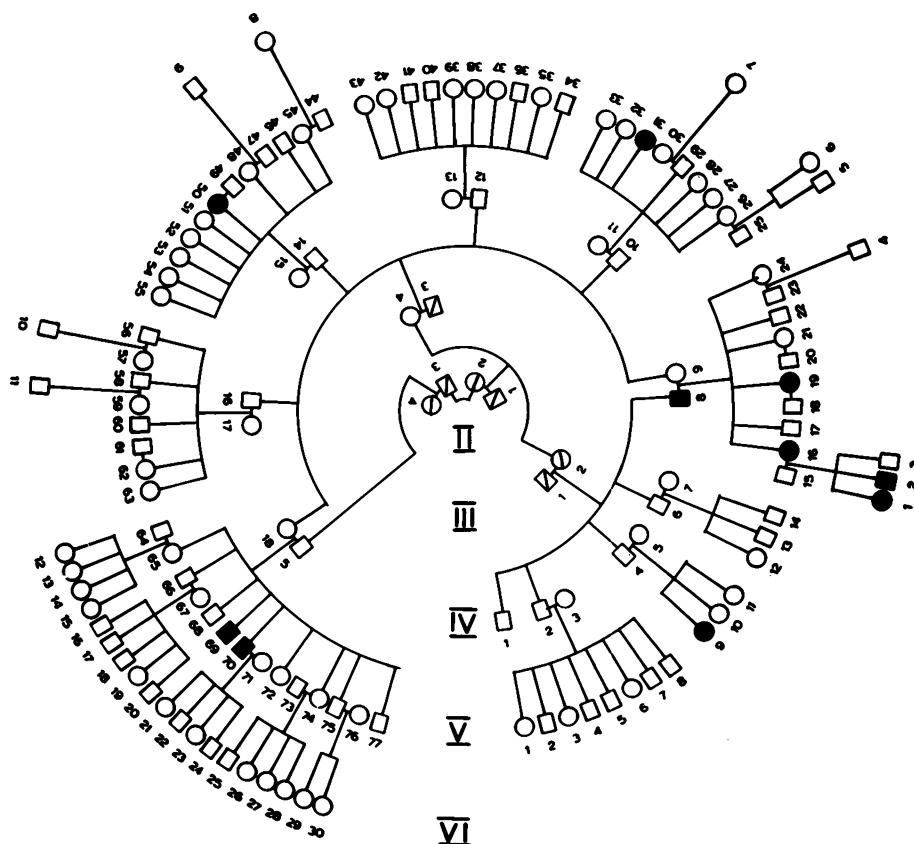


FIG. 1 Pedigree of Lebanese family.

1. Benedict's qualitative test (Flynn, Harper and De Mayo, 1953).
2. Cold Benedict's test at room temperature for 16 hours (Lasker and Enklewitz, 1933).
3. Bial's test (Harrison, 1947).
4. Tauber's test (Tauber, 1937).
5. Osazone test (Harrison, 1947).
6. Fermentation test (Harrison, 1947).
7. Paper chromatography (Horrocks and Manning, 1949).

For chromatography pure arabinose, *D*-fructose, *D*-glucose, *D*-glucuronolactone, *D*-glucuronic acid, *L*-xylulose and *D*-xylose were used as standards. A mixture of *D*-glucose, *D*-glucuronolactone, *D*-glucuronic acid and *L*-xylulose was added to each urine and run parallel to the untreated urine. The various reducing substances were chromatographed (descending) in butanol-pyridine-water (3:1 :1.5) and located by benzidine.

Blood and saliva specimens were collected for blood typing and for determination of salivary secretion of ABH substances.

RESULTS

Figure 1 shows that the family stems from two sisters, III-2 and III-4. As demonstrated by chromatography, 10 (four males and six females) of their 103 direct descendants excreted xylulose.

Three cases were examined during childhood (V-9, VI-1 and VI-2) and are

of particular interest. During the four year period of this investigation the initial tests on these children gave negative results, but *L*-xylulosuria appeared subsequently. V-9 was first examined at the age of 6 years. All tests were negative including those on samples obtained August 30, 1957 when she was 8 years old. On re-examination four days later the tests indicated the presence of a pentose and xylulose was present on chromatography.

In VI-1 all tests were negative at the age of 5 years. On re-examination at the age of 7, Bial's, Tauber's and the osazone tests gave positive reactions, but the other tests including chromatography were negative. These anomalous reactions may be due to the presence of a reducing substance other than xylulose. However, four months later the chemical tests indicated the presence of a pentose, and xylulose was detected by chromatography.

VI-2 was examined at the age of 2 years and 3 years, and all tests were negative. At the age of 4 years Bial's and the osazone tests were positive, but other tests including chromatographic analysis were negative. During the following four months all tests for pentose became increasingly positive, as did also the amount of xylulose detectable by chromatography. It would appear, therefore, that *L*-xylulosuria is not necessarily present at birth, but may develop and become demonstrable only later in life.

In three of the seven adults the excretion of *L*-xylulose was constantly demonstrated by chemical tests and chromatography, but in the remaining four cases the chemical tests gave doubtful results and xylulose was not always detected on chromatography. All 24 subjects who had married into the family gave negative results for *L*-xylulose.

All examined members of this family were tested for blood groups of the ABO, Rh, MN, P, Kell, Duffy and Lewis systems and for salivary secretion of ABH substances. No evidence of linkage of the urinary excretory trait with any of these genetic systems was disclosed.

DISCUSSION

The mechanism of this metabolic disorder has been adequately described (Eisenberg, Dayton and Burns, 1959; Wostenholme and O'Connor, 1959; Touster, 1959, 1960). Although *L*-xylulosuria is a harmless condition not requiring treatment, it is important that it should not be confused with diabetes mellitus. Three members of this family with *L*-xylulosuria have had glucose tolerance tests with normal results.

It is of great interest to note that in this family not a single positive result for xylulose was obtained in infancy and that the condition was only detected some years later. Whether the condition may be present at birth is unknown. It is also of interest that the excretion of *L*-xylulose in this family showed fluctuations, unlike the condition as described in Jews. In only three cases was *L*-xylulose present on every occasion. In the others the degree of reaction obtained from the tests and the amount of *L*-xylulose demonstrable on chromatography varied considerably and was sometimes undetectable during the four year period of this investigation.

Some members of the family were negative for *L*-xylulose but showed other reducing substances. These unidentified reducing substances were also present

on chromatography in the urines of the *L*-xylulose excretors. *L*-xylulose has been shown to be an intermediate in the glucuronic acid oxidation pathway. These other reducing substances may prove to be other intermediates, and if these are regarded as an expression of the anomaly the number of positive cases would be extended.

Bock (1944) reported a preponderance of males in the total number of reported cases. In this family there were four affected males and six affected females. This discrepancy between Bock's finding and ours could be explained by the fact that no comparable family investigation of this size has been previously reported.

Soon after the first cases were discovered, it was recognized that urinary excretion of *L*-xylulose is a familial anomaly. On the basis of 37 personally observed cases in 20 families, Lasker, Enklewitz and Lasker (1936) postulated that the condition was due to a recessive gene.

The manifestation of *L*-xylulosuria in this family could represent either (a) the homozygous state of a recessive gene, or (b) the heterozygous state of a dominant gene with poor penetrance.

Consanguinity of the parents for two of the seven sibships containing affected individuals would seem to favor the hypothesis of recessive inheritance. However, this could be coincidence in a community which is small and where consanguineous marriage is common, as is the case in the Lebanese families in Johannesburg. It should be noted that the recessive hypothesis would require the marriage into the family of five unrelated heterozygotes, namely III-1, IV-5, IV-11, IV-15 and V-15. This would be reasonable only if the gene has a rather high frequency in the population from which these mates were drawn. Dr. Margaret Lasker (personal communication) has suggested that the postulated recessive gene might have a high frequency in certain populations; she knows of six families in which *L*-xylulosuria occurred in two successive generations without known consanguinity of the parents.

The hypothesis of a dominant gene is favored by the transmission of *L*-xylulosuria from parent to child in three successive generations (IV-8 to V-16 and V-19; V-16 to VI-1 and VI-2). This interpretation would require that the gene be transmitted by five individuals who were tested and found normal (III-4, IV-4, IV-10, IV-14 and either IV-18 or III-5) and at least one deceased ancestor whose condition is unknown (III-2). The known occurrence of *L*-xylulosuria in more than one generation of other families could also be argued as favoring the concept of a dominant gene with reduced penetrance.

It should also be noted that *L*-xylulose was found in all specimens examined for only three of the 10 affected members of this family. If the excretion of *L*-xylulose is intermittent, it is possible that excretors may not have been detected, even though repeated examinations were done over a period of four years. We suggest, therefore, that the abnormal genotype, whether homozygous recessive or heterozygous dominant, is not always associated with the presence of detectable amounts of *L*-xylulose in the urine.

A clear distinction between the recessive and dominant hypotheses cannot be made on the basis of the information provided by this family alone. Acceptance of the recessive hypothesis would involve considerable assumptions, and

we therefore favor the hypothesis that *L*-xyluluria in this family is due to a dominant gene with poor penetrance.

SUMMARY

Ten cases of *L*-xyluluria were found among 127 members of a Lebanese family investigated over a period of four years. The parents of two of the seven sibships containing affected individuals were consanguineous.

Three cases were children when first examined and at first showed no evidence of the defect which only manifested itself later in childhood.

The mechanism of inheritance in this family appears to be that of a dominant gene with reduced penetrance.

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