Hereditary Factors in Adiposis Dolorosa (Dercum's Disease)

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ADIPOSIS DOLOROSA (Dercum's disease) is a condition wherein the chief clinical manifestations include obesity and painful subcutaneous lipomata. This combination was first described by Dercum (1892) in three patients. It is of interest that the patients were all females and a detailed family history in each case was negative.

A review of the literature to date is noteworthy for a paucity of patients with a positive family history. The only familial report we have been able to obtain is that of Keusch (1936) who recorded the disease in two sibs. Gates (1946) was impressed with the frequency of occurrence in females and expressed the thought that further elucidation in the manner of inheritance was required. Steiger, Litvin, Sasche and Durant (1952) described adiposis dolorosa in postmenopausal females with onset between the ages of 35 and 50 years. The possibility of a specific endocrine factor of etiologic importance was considered, but an endocrine survey was inconclusive. Winkelman and Echel (1925) suggested that a "pluriglandular" involvement is present. They based this suggestion upon a detailed necropsy study of their own and a review of 15 additional necropsy reports from the literature. They further noted a high frequency of interstitial neuritis in the nerve filaments of the fat nodules and speculated that this finding might well provide the basis for the sensation of pain in this condition. It is of interest that 12 of the 15 postmortem cases reviewed were females and their own case was also a female. They stated that the condition occurs five times as frequently in females as in males. The only therapy thus far of value has been surgical excision of the most symptomatic lipomata and weight reduction when indicated.

MATERIAL AND METHODS

The purpose of this investigation was to study the mode of inheritance of adiposis dolorosa and to gain further knowledge of the range of phenotypic expression of the gene through medical appraisal of all surviving members of two families where this disease is manifest. The two families were extensively investigated after confirmation of the diagnosis of Dercum's disease in the respective propositi. Diagnosis was based upon a careful history of the onset and development of painful subcutaneous nodules and a detailed physical examina-

Received December 10, 1962.

Presented at the meeting of the American Society of Human Genetics, Corvallis, Oregon, August 31, 1962.

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tion. Tissue was then obtained for pathologic examination. All available relatives were subsequently examined and records of pathologic examination of subcutaneous nodules were obtained if available.

RESULTS

Family A: The proband (Fig. 1, III-2) is a 26 year old white man who

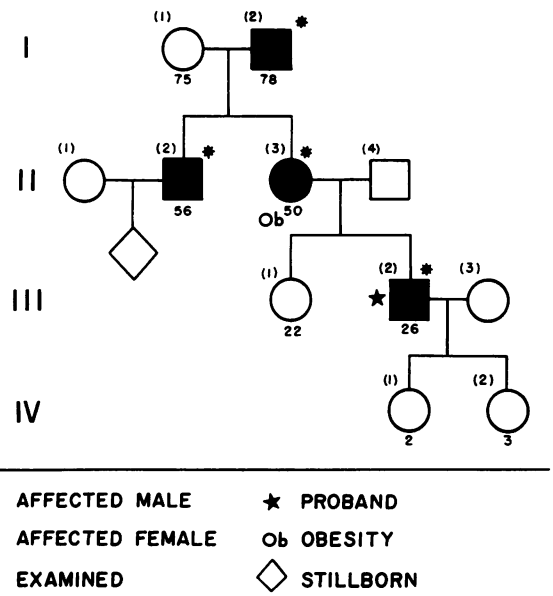

FIG. 1. Pedigree of family 1.

presented with a complaint of severely painful nodules, numbness, and weakness of the upper extremities. The onset of these complaints was at age 20 and signs and symptoms have been progressive since that time. Some 150 lipomata had been surgically excised during three hospitalizations. He still had many subcutaneous nodules over the entire body with the exception of the head. The nodules were more prominently distributed over the extremities and gluteal region and measured approximately 2 x 2 cm. in size. He had difficulty in assuming a position of comfort since pain was readily evoked by light palpation over the nodules. The patient was not obese. There was sensory loss over the ulnar nerve distribution bilaterally, secondary to lipomata impinging upon this nerve in the olecranon region. There was no significant motor deficit. The remainder of the physical examination was within normal limits. Pathologic specimens of the subcutaneous nodules were interpreted as being benign lipomata. Fig. 2 is a general view of the proband, and Fig. 3 shows the nodules in greater relief.

Positive diagnoses of adiposis dolorosa were also made on the proband's mother (Fig. 1, II-3), who was quite obese, his maternal uncle (II-2), and his maternal grandfather (I-2). Fig. 4 shows the maternal grandfather and careful inspection reveals the presence of nodules, particularly on the volar surfaces of the arms and on the anterior surface of the abdomen. The mother, uncle and

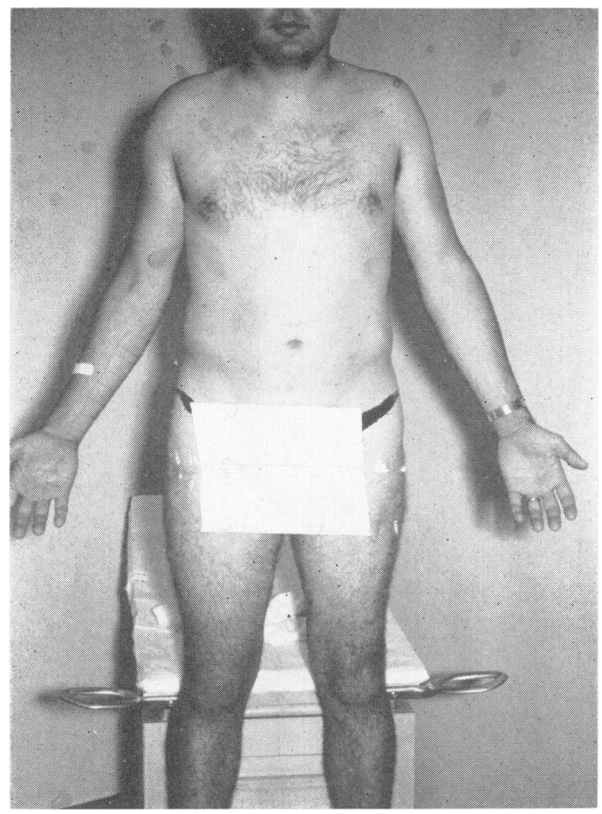

FIG. 2. View of proband, family 1. Note absence of obesity and mapping on right arm illustrating sensory impairment over the ulnar nerve distribution.

grandfather had fewer subcutaneous nodules than the proband, and symptoms of pain were of lesser magnitude, but definitely present.

Family B: The proband (Fig. 5, II-3) is a 49 year old white woman who is markedly obese. Painful subcutaneous nodules first appeared at age 45 and pain has since been progressive. She had a cholecystectomy in 1958 because of cholelithiasis. On physical examination there was marked obesity and multiple large painful subcutaneous nodules, measuring approximately 4 x 4 cm., were distributed over the entire body except for the head. On histologic examination one of the lesions showed the characteristics of a benign lipoma.

The proband's mother (Fig. 5, I-1) was markedly obese and had painful subcutaneous lipomata. The proband's two brothers (II-1 and II-2) also have subcutaneous lipomata, but these are not painful to palpation. Their physical examinations were otherwise within normal limits and they were not obese.

DISCUSSION

This is believed to be the first investigation wherein sufficient information has been obtained to justify postulation of the mode of inheritance of adiposis dolorosa, at least in two families.

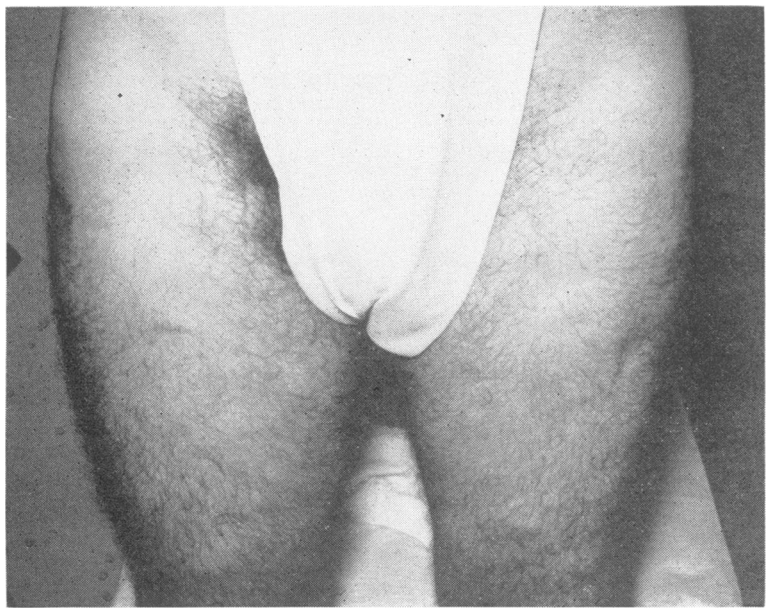

FIG. 3. Close up of subcutaneous lipomata over the anterior thighs.

Examination of the pedigree of Family A (Fig. 1) shows that Dercum's disease has been transmitted from parent to child through three generations. In Family B an affected mother transmitted the condition to all three of her children. Both males and females are affected, and sex-linkage is ruled out by the transmission of the disease from father to son in Family A. These findings suggest that adiposis dolorosa in these families is caused by an autosomal dominant gene.

The historical and physical findings suggest that there is variable expressivity of the postulated gene. The only individual with obesity in Family A is the mother of the proband. Symptoms of pain are considerably less manifest in the mother, the uncle and the grandfather than in the proband. In Family B both affected females are markedly obese and present the full clinical manifestations of the disease, while the males show only subcutaneous lipomata without the addition of pain. The range of clinical variation and the pattern of transmission therefore suggest the action of a dominant gene with variable expressivity.

In view of the marked obesity of the female members of both families, a sex-influenced factor cannot be excluded. This might well be an endocrine factor operative only in females which enhances the expression of the gene and produces obesity. This is certainly suggested by the marked obesity of affected females and the normal habitus in affected males, but our data are not extensive enough to exclude the effect of chance. However, if we couple these findings with those in the literature, we note a frequency of the disease in females 5 to 6 fold greater than that reported in males. Virtually all of the reported females have been markedly obese. Our findings show that the expression of the disease is frequently mild in males, and many such individuals would not be recognized unless very careful physical examinations were conducted. Hence, we postulate

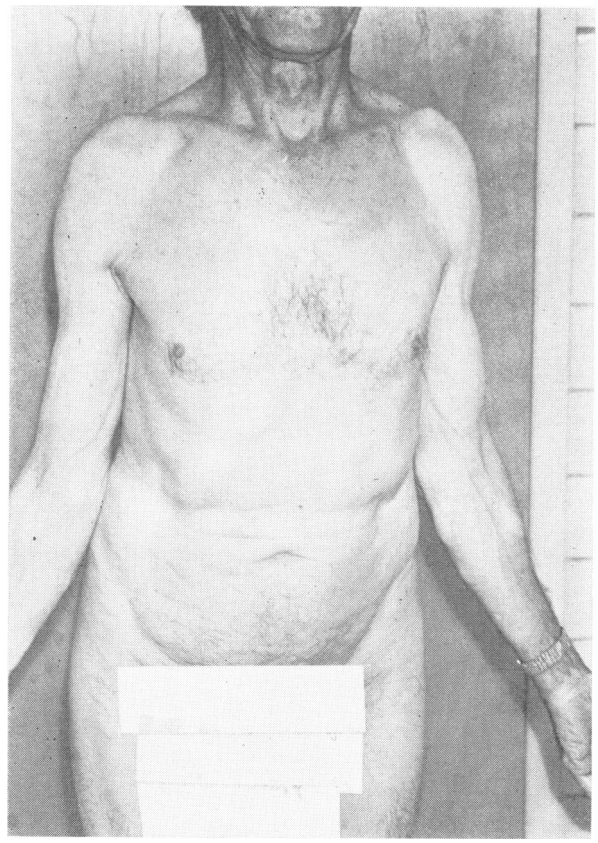

FIG. 4. Maternal grandfather of the proband, family 1. Note presence of subcutaneous lipomata over arms and torso.

a factor potentially critical for sex to account for the apparant sex disparity in this condition. Unfortunately, there have not been enough family studies to date to permit evaluation of this hypothesis.

The broad spectrum of manifestations of adiposis dolorosa as seen in these families, ranging from extreme obesity with intensely painful nodules to completely asymptomatic subcutaneous lipomata without obesity, emphasizes the need for detailed evaluation of every member of the family. Had the brothers of the proband in Family B been examined without benefit of knowledge of the diagnosis of adiposis dolorosa in their sister and mother, they almost certainly would have been diagnosed as manifesting familial lipomatosis, when in fact they represent a forme fruste of Dercum's disease. In the light of this, it might be wise to re-evaluate families in which familial lipomatosis has been diagnosed for the possible presence of individuals with manifestations of Dercum's disease. Similar ranges in phenotypic variation have been found in a number of diseases (*e.g.*, McNutt, Klingman, Lynch and Harlan, 1960). Such studies have shown that only through meticulous examination of each individual in the family can we assess the true mode of inheritance and comprehend the many subtle features of the condition which might otherwise be overlooked. The reasons for such

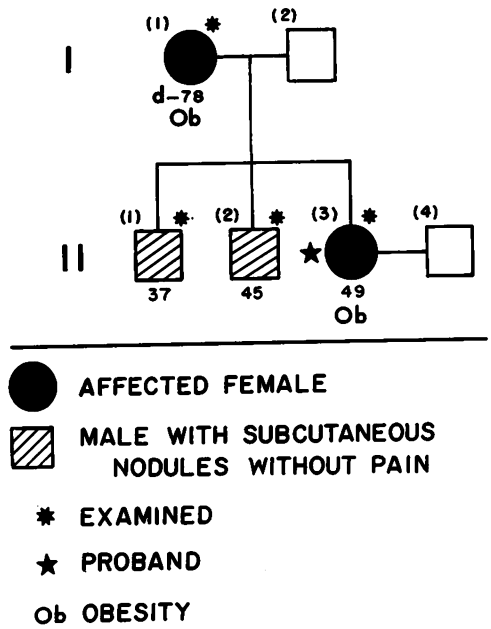

FIG. 5. Pedigree of family 2.

phenotypic variations of hereditary diseases are not completely clear. Such variation may be due, in part, to the action of the gene in differing biochemical milieu, to the presence of so-called modifying genes, or to environmental differences.

It seems clear that in the two families here described adiposis dolorosa may be ascribed to the action of a dominant gene with variable expressivity. However, most of the reports in the literature describe only a single case, and usually do not mention examination of relatives. It is entirely possible that affected relatives with minor clinical forms of adiposis dolorosa may have been overlooked in some previous studies because of lack of systematic examination of relatives. It is also possible that some apparently sporadic cases may represent new mutations to the postulated dominant gene. However, our experience with this disease is limited and we cannot exclude the possibility that an unknown proportion of sporadic cases may represent a different etiology.

SUMMARY

Two families with adiposis dolorosa (Dercum's disease) have been studied. In one family there are four cases in three generations, and in the second family there are four cases in two generations. The findings are interpreted as indicating the action of a dominant gene with variable expressivity. An hypothesis is advanced concerning the possible role of a sex-influenced factor.

ACKNOWLEDGMENT

Appreciation is extended to Dr. Calvin Davis for his critical evaluation of the manuscript and to Dr. A. M. Pantano for cooperation with the second family in this study.

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