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THE GENETIC AMYLOIDOSES WITH SPECIAL EMPHASIS ON FAMILIAL MEDITERRANEAN FEVER*

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IT IS A GREAT pleasure to talk about Familial Mediterranean Fever (FMF) here in Detroit where the disease is familiar to physicians. Therefore, I will not go into details about the clinical picture of the disease, which I trust you know as well as we. I shall talk about FMF as one of the genetic amyloidoses and stress in passing only those clinical aspects which apparently are more obvious in Israel.

By way of introduction, I would like to say a word about the incidence of amyloidosis. Usually considered a rare disease, it has been reported in between 0.5 to 0.8 per cent of autopsies. However, we have recently taken blocks of 200 consecutive autopsies at our hospital, in which amyloidosis was not diagnosed, and among these found amyloid deposits in 28 including two cases of generalized amyloidosis. I would also like to recall the experience of Dr. Teilum, Professor of Pathology in Copenhagen.[5] On reviewing, from his own department, 28 autopsied cases of rheumatoid arthritis in whom the diagnosis of amyloidosis had been made in only 3 he found amyloid in 14 additional ones. This proves that amyloid is not just found; it must be looked for, and when looked for, it is not so rare after all. The true incidence of amyloidosis is certainly much higher than has been suspected.

One reason we found more cases than usual is a technique which we learned from Dr. Hans-Peter Missmahl of Tübingen, Germany.[4] This calls for the staining of amyloid tissue by Congo red and examining with the polarized-light microscope. With this technique, we frequently were able to identify with certainty amyloid deposits not detectable by ordinary microscopy and thus to establish the diagnosis of amyloidosis. This was of special help in the examination of biopsy material.

When a physician thinks or speaks about amyloidosis he usually conceives of it as being secondary to some chronic infectious or inflammatory disease. When we encountered our first FMF patient with amyloidosis, it seemed logical to assume that the amyloidosis was secondary to the many attacks of fever he had suffered.

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However, it was not long before amyloidosis was found in another patient very shortly after the onset of his attacks, and finally our experience broadened to include a patient who had never had attacks (his brother suffered from attacks) and in whom amyloidosis appeared as the sole manifestation of FMF. These observations led to the conclusion that the amyloidosis in FMF is not secondary but hereditary.

There are today five entities of genetic amyloidosis and it is likely that in the future additional entities will be described. This morning I shall review the genetic amyloidoses described so far and suggest some sort of classification.

The inherited amyloidoses are systemic involving all organs of the body with few exceptions. Nevertheless, the disease usually becomes manifest clinically through the more massive involvement of one organ. Accordingly, they can be divided into three types: the *nephropathic* types in which the main symptoms and signs are those of renal disease; the *neuropathic* forms in which peripheral neuropathy is the principal feature; the *cardiopathic* type which is marked by intractable heart failure.

I shall start with FMF which is a nephropathic amyloidosis. FMF is an ethnically restricted disease. As you know, the Jewish population is divided in its ethnic origin into Ashkenazi and Sephardi Jews. In Israel, each of these groups comprises about 50 per cent of the population. Nevertheless, our 400 patients include only nine Ashkenazi, all the others being Sephardi Jews who derive from various countries around the Mediterranean; there are five Arabs, all born in Israel. It is not so astonishing that most of our patients in Israel are Jews. However, a review of the literature will show that the largest group (more than 50 per cent) are again non-Ashkenazi Jews; the remainder include a large group of Armenians, a small group of Arabs and sporadic cases of other origins. All of them derive from Mediterranean countries.

A disease which is ethnically restricted, unless it is due to some infectious or nutritional factor, is usually a genetic disease. In FMF we have shown that the disease is transmitted as a complete autosomal recessive. A positive family history was obtained in 229 of 400 patients and a questionable one in 75. In the vast majority of cases only sibs are affected, and we find that of 215 marriages producing FMF offspring, 42 were cousin marriages. Thus, we find all the characteristics of recessive inheritance, as has also been shown by other techniques. The gene frequency is 0.02 in the Sephardi Jewish population.

FMF becomes clincially manifest very early in life. By the age of 15, about two-thirds of the patients are already affected and by the age of 20, more than 30 per cent. It seems likely that most of the remainder probably experience some sort of attacks in childhood, but the disease is not recognized at that time. It is of interest to note that our youngest patient developed his first attack when one month old.

The attacks of FMF consist of short bouts of fever accompanied by abdominal pain, by chest pain or by joint manifestations. Although attacks as a rule subside in

24-48 hours, we have observed rather frequently the protraction of a usual joint attack into a chronic monoarthritis, which may persist for weeks and even months. It is a characteristic feature of the arthritis of FMF that even if the patient develops hydroarthrosis and is immobilized for weeks or months, the inflammatory changes eventually resolve and the patient regains complete use of his joints. Another feature which I believe is characteristic of FMF is a skin manifestation which we call erysipelas-like erythema. It usually appears in the ankle region, frequently after strenuous exercise, and subsides in 12 to 24 hours.

As to the amyloidosis, we have examined 330 patients. Of these, 53 have died of amyloidosis while 50 are living today with nephropathy; in 23 of the later amyloid has been demonstrated by rectal biopsy.[1,2,3]

The duration of the nephropathy from the time of diagnosis to death is usually 6 to 10 years. There is a large group who died earlier, but these came under observation when they already had progressive renal disease. We know today that there is a pre-clinical stage of amyloidosis. In one of our patients kidney biopsy was performed and found positive for amyloid, in spite of the fact that she presented no clinical or laboratory evidence of renal disease or other manifestations of amyloidosis. Three years passed from the time of biopsy to the appearance of proteinuria. There is, therefore, a prolonged pre-clinical stage in amyloidosis of FMF and probably in the others as well.

Most of our patients are very young. Two-thirds are below the age of 30, and 80 percent below 35. The age of death from amyloidosis is also very early. Our youngest patient was six years old when he died. It is interesting to note that the cause of death in all of our FMF patients was amyloidosis, except for one who was killed in a road accident.

We now have five patients who have never shown attacks of FMF prior to the appearance of amyloidosis. However, each of them has a sibling or offspring who shows classical FMF attacks. We believe that there are two phenotypes of FMF: Phenotype I, in which attacks precede the onset of amyloidosis and phenotype II, in which amyloidosis appears first and clinical attacks appear later or not at all.

A few years ago, Drs. Muckle and Wells[6] from England described a family in which 9 of 18 members in three generations were affected by a curious disease characterized by bouts of fever, urticarial skin rash, progressive deafness and renal disease due to amyloidosis. The transmission in this family was a dominant one, death occurring from renal failure between the ages of 40 to 45. This then is the other example of nephropathic genetic amyloidosis.

A myocardiopathic amyloidosis was described in Denmark last year in a family in which 8 of 12 siblings were affected. Fatigue, dyspnea and intractable heart failure appeared between the ages of 40 and 50. The patients died two to five years after the onset of symptoms. Transmission is probably dominant.

Two types of neuropathic amyloidosis are known today. One has been described by various Portugese authors, notably Andrade and Horta,[7] who have observed to date more than 100 cases. In those affected, a dominantly transmitted gene causes severe manifestations leading, after five years, to death. The manifestations are predominantly of a peripheral neuropathy affecting first and most severely the lower extremities, and later the gastrointestinal tract.

Another form of neuropathy has been reported from America by Rukavina and his group.[8] Manifestations start in the upper extremities often with a carpal tunnel syndrome, and the disease, which is also dominantly transmitted, progresses much more slowly than the Portugese variety. An interesting and probably pathognomonic feature is the presence of opacities composed of amyloid material in the vitreous body of the eye.

An enumeration of the genetic amyloidoses according to their presentation as nephropathy, cardiopathy or neuropathy is presented in Table I.[9]

FMF and the Portuguese form of amyloid neuropathy are ethnically restricted. It is also of interest to note that the cardiopathy and the two neuropathies produce symptoms which are due exclusively to amyloid deposition in the tissues; whereas, in the nephropathic forms (FMF and the syndrome of Muckle and Wells) there are pleiotropic manifestations of the gene. These are symptoms and signs which are independent characters of the mutant gene but are not directly related to the formation of amyloid.

I must say a few words concerning the histology of amyloidosis. We all know, I am sure, the classical distinctions between typical and atypical amyloidosis, which assume that typical amyloidosis is of the secondary type and atypical the primary type. This has been used in various classifications, but in practice it has been shown that there is no close correlation between primary and atypical on the one hand, or typical and secondary on the other.

Table I
THE GENETIC AMYLOIDOSES

Clinical Varieties	Histological type	Mode of inheritance	Ethnic predilection
NEPHROPATHY			
1. Familial Mediterranean Fever	Peri-reticulin	Recessive	Mediterranean Jews and Armenians
a) Phenotype I: Attacks first			
b) Phenotype II: Amyloidosis first			
2. Fever, rash, and deafness	" "	Dominant	?
CARDIOPATHY	Peri-collagen	" (?)	?
NEUROPATHY			
1. Legs most affected	" "	"	Portuguese
2. Arms most affected	" "	"	None

We have examined 70 cases of amyloidosis of the various syndromes including all five genetic entities. This was carried out a short time after Dr. Missmahl published two cases of amyloidosis in which he claimed that in each the mode of deposition of amyloid was different histologically. The difference is this: In one case he found the amyloid deposited close to the lumen of the arterioles, in the intima and the media, where reticulin fibers are usually very numerous. In the second he found amyloid mainly in the adventitia where collagen fibers normally predominate. We examined, as I said, 70 cases with him at our laboratory and came to the conclusion that not only has every case of amyloidosis either a "peri-reticulin" or a "peri-collagen" distribution, but also every clinical entity of amyloidosis is homogeneous in this respect, belonging either to one or the other group.

Amyloidosis is a disease of tissue systems and is not limited to specific organs. In the one variety, amyloid is deposited throughout the body where reticulin fibers are numerous; whereas, in the other the collagen fiber is primarily affected.

Fig. 1. is a graphic description of the two varieties. It shows that peri-reticulin amyloid is initially deposited in the intima and later spreads centrifugally. Peri-collagen amyloid is first deposited in the adventitia and spreads centripetally, leaving the intima free.

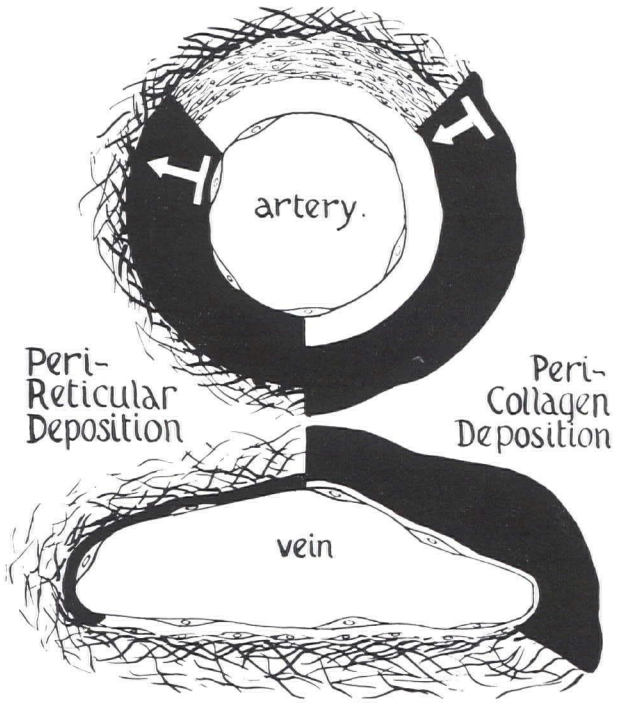

Figure 1

The vascular lesion in peri-reticulin and peri-collagen amyloidosis (reproduced from Harefuah 64:41, 1963). (White line behind the arrow indicates site of the initial amyloid deposition.)

As to the classification of amyloidosis, our suggestion is based upon histological and etiological criteria (Table II). Of the genetic amyloidoses, two are of peri-reticulin and three of peri-collagen distribution. Of the various entities of secondary or acquired amyloidosis, all except that of multiple myeloma and macroglobulinemia are of the peri-reticulin variety. The idiopathic forms include those cases in which no lesion other than amyloidosis was found on autopsy, and the etiology is unknown.

We urge that a distinction be made between "primary" and "idiopathic amyloidosis. Primary should best be an anatomopathological term only, connoting no more than that amyloidosis is the sole autopsy finding. A case of primary amyloidosis may be of known or unknown etiology. If it is a genetic amyloidosis, etiology is known though pathogenesis is not. It is probable that many cases of so-called idiopathic primary amyloidosis are sporadic examples of the genetic type. In such cases, a complete family history and evaluation of a pedigree is indicated and sometimes, as has happened, a genetic amyloidosis will be established.

SUMMARY

The pathogenesis of amyloidosis is still unknown. It has been variously assumed to be due to antigen-antibody reaction, to various deposits from the blood, and so on. None of these theories have been proved. I would like to conclude with a few words regarding our hypothesis on the pathogenesis of amyloidosis, which is based, mainly on 3 facts:

1) Amyloid occurs throughout the body in connective tissue and has never been found in any other tissue.

2) Amyloid is a fibrous protein, as has been proved by polarized-light and electron microscopy.

3) Amyloid is initially deposited in relation to pre-existing connective fibers, either reticulin or collagen.

Table II

CLASSIFICATION OF THE AMYLOIDOSES

	PERI-RETICULAR	PERI-COLLAGEN
Hereditary	Familial Mediterranean Fever Urticaria and Deafness (Muckle & Wells)	Neuropathic (Rukavina et al) Neuropathic (Andrade; Horta) Cardiopathic (Frederiksen et al)
Acquired	Assoc. with Chronic Infection (tuberculosis, osteomyelitis, etc.), Chronic Inflammation of Unknown Etiology (Rheumatoid arth., etc.), Malignant Neoplasms	Assoc. with Multiple Myeloma
Idiopathic	Nephropathic ("typical distribution")	"Classical" Primary Neuropathic Cardiopathic

Therefore we believe that amyloid is in some way related pathogenetically to the connective tissue and to the normal fibrous proteins — probably reticulin and collagen. It is tempting to assume that amyloidosis is an aberration of those cells, which in health form the normal fibrous proteins and go astray as the result of some inborn or acquired defect and form amyloid. Of course, this is speculation awaiting proof. We do believe, however, that the recognition of five clear-cut entities of genetic amyloidosis will certainly be helpful in the concept and also in the final elucidation of the pathogenesis of amyloidosis.

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