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Quantitative Studies of Amyloid in the Islets of Langerhans

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ABSTRACT

The relationship between the degree of amyloidosis in pancreatic islet tissue and the frequency of islets containing amyloid was studied in an autopsy material. A very strong positive correlation was found between these two variables in both the head and the tail of the pancreas. There was also a positive correlation between the degree of amyloidosis in islets containing amyloid and their frequency. This may indicate that the deposition of amyloid in the islets of Langerhans is a continuous process affecting progressively increasing numbers of islets. It is probable that the amyloid formation in the islets is influenced by some factor or factors that affect the different islets to different degrees. It is conceivable that one such factor may be vascular changes. The strong correlation between the frequency of islets containing amyloid and the degree of amyloidosis can be utilized as a simple and rapid method of determining the latter.

INTRODUCTION

Deposition of amyloid in the islets of Langerhans is a common occurrence in elderly persons, especially diabetics. In spite of the fact that 70 years have elapsed since amyloidosis of the islets was first described (8), its cause and mechanism of development are still essentially unknown (11). The amount of amyloid varies greatly between different cases and between the different islets in the individual case (6). The reason for this difference in the amyloid content between different islets even in the same person is not clear. Certain observations suggest, however, that the formation of amyloid in the islets is influenced by some factor or factors which affect the different islets to different degrees. Thus it has been found that amyloid-containing islets occur particularly in areas of lipomatosis and fibrosis (6), and that there is a smaller number of such islets in the pancreatic head than in the tail (Westermark, to be published).

The present investigation was carried out as a contribution to the attempts at determining what factor or factors are of importance for the development of amyloidosis of the islets. Its aim was to find out whether this occurs quite randomly or whether its progress conforms to any definite law.

MATERIAL AND METHODS

The material consisted of pancreatic tissue taken at autopsy from 17 patients with known amyloidosis of the islets. The composition of this material has been described in detail in a previous paper (12). Ten of the patients had diabetes mellitus of maturity onset type while 7 had no known diabetes. Pieces of tissue from the head and tail of the pancreas were fixed in a mixture of equal parts of 4% lead subacetate and 4% formaldehyde solution (9), in carbon dioxide-free water.

After embedding in paraffin, a section about 4 μm thick was cut from each piece of pancreas and was mounted on a slide. The section was deparaffinized, treated with 0.1 N HCl for about 5 min and then stained with alkaline Congo red (10). An adjacent section was stained with alcian blue, pH 1 (4) and then with van Gieson stain. The Congo red stained sections were examined in a polarization microscope. In this examination both islets showing amyloid deposits and the total number of islets were counted. The degree of amyloidosis, i.e. that part of the total islet area that was occupied by amyloid, was determined on the alcian blue – van Gieson stained section. Details of this determination have been given in the previous report (12). The mean area occupied by amyloid in islets with amyloid deposits was also determined on this section. In this determination all islets that completely lacked amyloid deposits were thus excluded.

In order to find out how the amyloid was distributed in the islets, whole islets were studied by serial sectioning. For this, 60 consecutive sections about 5 μm thick were prepared from 3 patients, 2 diabetics and 1 non-diabetic, and were stained with alkaline Congo red. The different islets were then followed from section to section.

RESULTS

The degree of amyloidosis in the islets and the frequency of amyloid-containing islets in the pan-

Table I

	Tail		Head	
	Islet amyloid in % of islet area	% involved islets	Islet amyloid in % of islet area	% involved islets
Diabetic				
1	11.4	86	8.0	64
2	0.9	12	1.5	11
3	43.1	99	21.2	78
4	29.8	90	5.2	57
5	4.8	41	0.5	8
6	2.6	33	0.2	6
7	22.9	92	29.4	83
8	49.5	98	46.3	94
9	0.6	7	0.1	2
10	46.8	100	20.2	93
Mean values ±S.E.M.	21.2±6.3	66±12	13.3±4.9	50±12
Non-diabetic				
1	0.3	3	0.0	0
2	1.5	30	0.1	2
3	0.6	3	0.0	0
4	20.5	90	9.9	53
5	0.9	30	2.3	22
6	0.2	2	0.0	0
7	1.8	12	0'0	0
Mean values ±S.E.M.	3.7±2.8	24±12	1.8±1.4	11±8

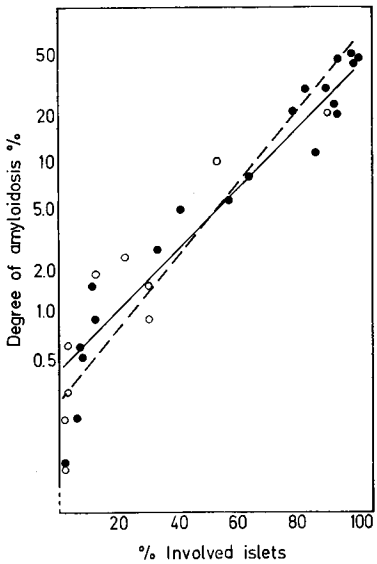

Fig. 1. Correlation between the degree of amyloidosis in the islets of Langerhans and the percentage number of islets containing amyloid in 10 cases of maturity onset diabetes mellitus (●) and 7 cases without diabetes (○). Head (– – –): $r = 0.95$; log $Y = 0.024X - 0.59$. Tail (—): $r = 0.96$; log $Y = 0.020X - 0.38$.

creatic head and tail are shown in Table 1. The degree of amyloidosis varied greatly from one case to another. Practically always, however, islets with no deposition of amyloid were found, even in cases with a high degree of amyloidosis. The 3 patients whose specimens were serially sectioned had different degrees of islet amyloidosis. Islets with amyloid deposits showed such deposits in all sections, except a very small number of islets in all three cases, where amyloid-negative sections were found in the absolute periphery of the islets. Amyloid-negative islets in which the section happened to lie more or less centrally never showed amyloid deposition in any other section. Even in mildly involved islets amyloid was found not as a small focal area but more as a more diffuse deposit along the capillaries.

A very strong correlation was found between the degree of amyloidosis in the islets and the frequency of islets containing amyloid (tail: $r = 0.96$; log $Y = 0.020X - 0.38$; head: $r = 0.95$; log $Y = 0.024X - 0.59$; Fig. 1). The regression lines for the head and the tail differed somewhat, but this difference was not significant ($P > 0.05$). In some cases the points lay relatively far from the regression lines. In an attempt to determine whether this finding could be due to the fact that in certain persons the process of amyloid deposition is not the same as in others, the correlation between the residuals was tested in those cases where both the head and the tail of the pancreas showed amyloid deposits. No significant correlation was found ($P > 0.05$).

In the non-diabetic patients with one exception, only mild degrees of amyloidosis were seen, while the diabetics showed a considerably larger variation. No other difference between diabetics and non-diabetics was seen in this study.

An increasing number of islets containing amyloid was associated with a higher degree of amyloidosis in the involved islets ($r = 0.53$, $P < 0.01$; Fig. 2). In some cases, however, the affected islets contained a large amount of amyloid even though they were few in number.

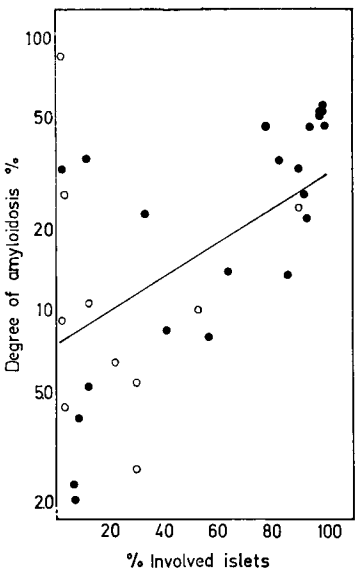

Fig. 2. Correlation between the degree of amyloidosis in islets with deposits of amyloid and the percentage number of islets containing amyloid. $r = 0.53$; $P < 0.01$. Diabetic cases (●) and non-diabetic cases (○).

DISCUSSION

The results of this study indicate that the deposition of amyloid in the islets of Langerhans takes place in conformity with a definite law. The correlation between the degree of amyloidosis in all islets and the frequency of amyloid-containing islets, and between the degree of amyloidosis in amyloid-containing islets and the frequency of such islets suggests that amyloid is first deposited in a few islets. When an increasing number of islets then become involved the amount of amyloid in the previously affected islets increases.

The correlation between the degree of amyloidosis and the frequency of islets containing amyloid deposits is very strong. The slope of the regression line for the pancreatic head differs somewhat from that for the tail. This difference is not statistically significant, however. Since there is no correlation between the residuals either, it is more probable that the deviations of the points from the regression lines are due to natural variation and errors of measurement.

While planimetric measurement of the degree of amyloidosis is very time-consuming, it takes little time to determine the frequency of islets containing amyloid deposits in a section. As the correlation between these two variables is very strong, it is possible to find out the degree of amyloidosis indirectly by determining the number of islets with and the number without amyloid deposits.

Amyloid is seldom found in all islets in a section. Serial sectioning studies in the present investigation showed that it was unusual for an islet that in one section contained no amyloid to show amyloidosis in other sections. It was thus established that islets completely free from amyloid occur in most cases. This finding supports the assumption that the formation of amyloid in the islets of Langerhans is influenced by one or more local factors. One such factor may be vascular changes. Some authors consider that there is a relationship between islet amyloidosis and arteriosclerosis in the pancreas (3, 6, 7), but this has been denied by other investigators (1, 2, 5).

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