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The sinoatrial node in familial amyloidosis with polyneuropathy

A clinico-pathological study of nine cases from Northern Sweden

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Summary. The pathogenesis of disturbances of the initiation and conduction of the cardiac impulse in cardiac amyloidosis has been a matter of controversy. In this study, we have analyzed the histopathology of the sinoatrial node and the atrial myocardium in nine cases of familial amyloidosis with polyneuropathy. Our results indicate that in this disease, amyloid infiltration of the sinoatrial node and the atrial musculature per se may account for the electrophysiological disturbances of these regions.

Key words: Amyloidosis – Sinoatrial node – Cardiac conduction disturbances

Introduction

Involvement of the heart is common in all forms of systemic amyloidosis, including the heredofamilial syndromes (e.g. Buja et al. 1970; Hofer and Andersson 1975; Kyle and Bayrd 1975). An important manifestation of amyloid heart disease is a high prevalence of disturbances of atrioventricular and intraventricular conduction (Buja et al. 1970; De Freitas and Barbedo 1978; Olofsson et al. 1980), while disturbances in the function of the sinus node seem to have been less frequent. In recent years, however, a number of patients with sinus node dysfunction and systemic amyloidosis have been reported (see James 1966; Schroeder et al. 1975; Ridolfi et al. 1977; Isokane et al. 1978; Gray et al. 1978; Bharati et al. 1980), including some with familial amyloidosis with polyneuropathy (FAP) (Olofsson et al. 1983). A high prevalence of atrial arrhythmias, mainly atrial fibrillation, has also been described in FAP (Olofsson et al. 1980).

The present investigation aimed to study the morphological basis of sinoatrial disease in FAP. We have studied clinical, electrocardiographic

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and histopathological features of the function of the sinus node in nine cases.

Material and methods

The hearts from nine individuals with well documented familial amyloidosis with polyneuropathy (Andersson 1970) were investigated. The diagnoses had been repeatedly confirmed *ante mortem* by clinical and histopathological investigations of skin and/or rectal mucosa, and *post mortem* by histological investigations of necropsy material.

The hearts were subjected to detailed macroscopic examination including weighing and examination of the valves and coronary arteries. The sinoatrial node was removed according to the method of Hudson (1963). About 30 sections from each sinus node were studied. Additional specimens were obtained from the lateral wall and the auricular appendage of the right atrium, and from the internodal atrial myocardium (cf. James and Sherf 1971; Janse and Andersson 1974). The specimens were fixed in neutral buffered formalin, embedded in paraffin and sectioned. Sections were interpreted as positive for amyloid when they showed positive dichroic birefringence after staining with alkaline Congo red. Adjacent sections were stained with elastic van Gieson.

The degree of amyloid deposition was graded on a scale of 0 to +++, ranging from none to severe (cf. Hofer and Andersson 1975).

Results

Patients

Essential clinical data of the nine patients included in this study are presented in Table 1. All had a clinical pattern characteristic of FAP. No chronic inflammatory diseases, myelomatosis or tumors were found in any of the patients. Five of the patients (nos. 1, 3, 4, 6 and 7) belonged to families of which several members also had established FAP, the other four (nos. 2, 5, 8 and 9) were considered to be so-called sporadic cases (see Eriksson et al. 1983).

Electrocardiograms recorded between one to eight months prior to death were available for all patients. No long term ECG recording was performed. Five of the patients (nos. 4, 6, 7, 8 and 9) showed evidence of dysfunction of the sinus node and/or atrial arrhythmias. All patients had concomitant disturbances of atrioventricular and/or intraventricular conduction.

Three patients were given pacemakers for complete heart block (nos. 3, 6 and 8) and one for atrial fibrillation with a slow ventricular rate (no. 7).

Two patients (nos. 6 and 7) had heart murmurs consistent with aortic stenosis. These two patients and patients nos. 4 and 8 had the symptoms and signs of congestive heart failure, and were treated with diuretics.

None of the patients had a history or ECG signs of recent or old myocardial infarction and none received cardiotropic drugs, except patient no. 7, who was given digoxin after implantation of a pacemaker.

Gross examination of the heart

The hearts appeared rubbery and firm on macroscopic examination. Six hearts (nos. 3, 4, 6, 7, 8, 9) were enlarged and weighed from 570 g to 835 g

Table 1. Clinical data in nine patients with familial amyloidosis with polyneuropathy

Patient no.	Sex	Age at death (years)	Duration of symptoms (years)	ECG	Clinical comments	Cause of death
1	M	43	11	LAFB	Polyneuropathy, malabsorption, cachexia	Pneumonia
2	F	65	7	First degree AV block, LAFB	Polyneuropathy, malabsorption	Pneumonia
3	M	78	3	Complete AV block	Polyneuropathy, syncope, (pacemaker)	Pneumonia
4	M	79	3	SA block/sinus arrest, Paroxysmal AF, RBBB	Polyneuropathy, malabsorption, cardiac failure	Cardiac failure
5	M	79	7	First degree AV block, RBBB	Polyneuropathy, malabsorption	Pneumonia
6	M	89	15	AF, Complete AV block	Polyneuropathy, syncope, aortic stenosis, cardiac failure, (pacemaker)	Cardiac failure
7	M	75	13	AF with slow ventricular rate, LBBB	Polyneuropathy, malabsorption, aortic stenosis, cardiac failure, (pacemaker)	Cardiac failure
8	M	76	5	Paroxysmal atrial flutter, Complete AV block	Polyneuropathy, malabsorption, syncope, cardiac failure, (pacemaker)	Pneumonia
9	M	77	5	Atrial flutter – AF, LAFB	Polyneuropathy, malabsorption	Pneumonia

AF = atrial fibrillation; AV = atrioventricular; LAFB = left anterior fascicular block; LBBB = left bundle branch block; RBBB = right bundle branch block; SA = sinoatrial

(mean 660 g). Three hearts (nos. 6, 7 and 8) exhibited calcification of the aortic valves with stenosis in two (nos. 6 and 7). Extramural coronary luminal narrowing was slight in all cases but one (no. 4), where it was moderate. The main results are summarized in Table 2.

Microscopic examination

Moderate to severe amyloid deposits were seen in the ordinary myocardium of all four chambers of all nine hearts. As in a previous study of the atrioven-

Table 2. Macroscopic and microscopic findings in nine hearts

Patient no.	Heart weight (g)	Main macroscopic findings	Amyloid infiltration				
			SAN	SAA wall/lumen		IAM	RA_A	RA_L
1	280	Normal	+++	+	P	+++	+++	+++
2	320	Normal	+++	+(+)	P	+++	+++	+++
3	585	General enlargement and dilatation. Pacemaker	+++	(+)	P	+++	++	++(+)
4	710	General enlargement	+++	+(+)	P	+++	+++	+++
5	290	Normal	+++	(+)	P	+++	+++	+++
6	580	General enlargement and dilatation. Moderate to severe calcification of aortic valves with stenosis. Pacemaker	+++	++	S	+++	+++	+++
7	835	Enlargement, especially of left ventricle wall. Severe calcification and stenosis of aortic valves. Pacemaker	+++	++	P	+++	+++	+++
8	665	Enlargement, especially of left ventricle wall. Slight calcification of aortic valves. Pacemaker	+++	(+)	P	+++	+++	+++
9	570	General enlargement	+++	(+)	P	+++	+++	+++

IAM = internodal atrial myocardium; RA_A = right atrium (auriculum); RA_L = right atrium (lateral wall); SAA = sinoatrial artery; SAN = sinoatrial node; P = pertinent lumen; S = slightly narrowed lumen

+ = slight amyloid deposits; ++ = moderate amyloid deposits; +++ = abundant amyloid

Brackets indicate subtle differences between the various grades, or an uneven distribution

tricular conduction system (Eriksson et al. 1983), the amyloid deposits were especially abundant in the subendocardium and subepicardium. Furthermore, they seemed somewhat more abundant in the atria than in the ventricles.

In the various parts of the right atrium, amyloid deposits were abundant, and appeared in nodular and filiform deposits, throughout the whole thickness of the atrial wall (Fig. 1). The amyloid often encircled individual myofibres, which were sometimes severely degenerated. No significant difference in the abundance of amyloid infiltration could be seen when the right auricu-

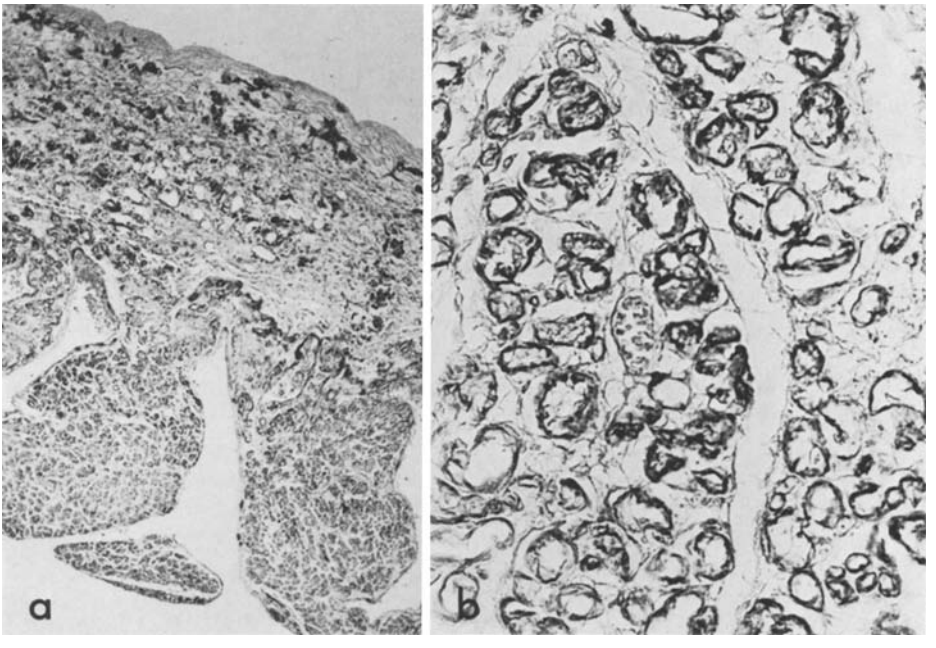

Fig. 1 a, b. Congo red stained cross sections of right atrial wall of patient 2. **a** Severe amyloid infiltration (*black*) in the subepicardium. × 40. **b** Amyloid is encircling individual muscle fibres of which many are degenerated and lost. × 250

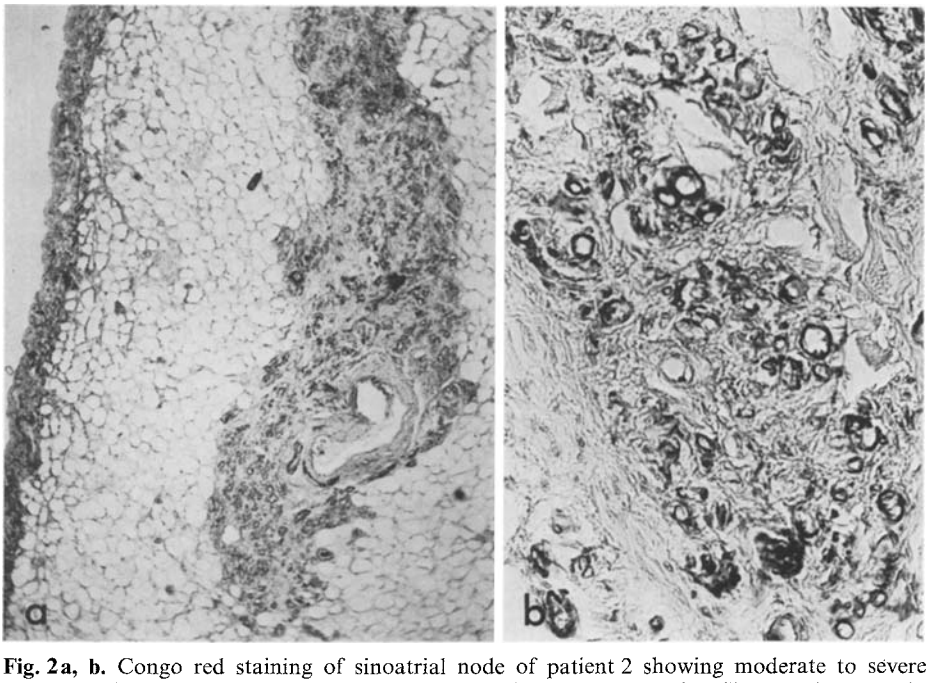

Fig. 2 a, b. Congo red staining of sinoatrial node of patient 2 showing moderate to severe amyloid infiltration (*black*). **a** The perinodal area is infiltrated by fat. Sinus node artery in the lower right corner. × 40. **b** Higher magnification illustrating amyloid deposits and loss of nodal fibres. × 250

lar appendage, the right atrial lateral wall, and the so called internodal atrial myocardium (Janse and Andersson 1974; cf. James and Sherf 1971) were compared.

In all the hearts examined, there was marked amyloid infiltration in the sinoatrial node (Fig. 2). Sometimes, the amyloid desposits seemed to be slightly higher up than in the surrounding atrial myocardium. When the amyloid was abundant, the deposits were mostly nodular or confluent, rarely filiform. At the same time the cells of the sinoatrial node were significantly reduced in number and had largely been replaced or dislocated by amyloid. Occasionally, there was fatty infiltration of the sinoatrial node and its surroundings (nos. 2 and 3). In one case (no. 7) a fresh haemorrhage was seen in and around the sinoatrial node.

As in intramyocardial vessels elsewhere, the sinoatrial artery usually exhibited slight amyloid deposits in its walls, but in no case was the lumen of the sinoatrial artery significantly obstructed by amyloid or by atherosclerosis.

Discussion

Cardiac amyloidosis occurs in all forms of systemic amyloidosis and is often associated with disturbances of atrioventricular and/or intraventricular conduction (Buja et al. 1970; Kyle and Bayrd 1975; Olofsson et al. 1980). There are few detailed histopathological studies of the conduction system in amyloid heart disease and they have reached conflicting conclusions concerning the cause of the disturbances in conduction. Some authors believe that amyloid infiltration of the conduction system per se causes these (James 1966), while others consider direct amyloid infiltration as being of minor importance (Davies 1971; Ridolfi et al. 1977).

While the above-mentioned studies have been dominated by cases with senile cardiac amyloidosis, there have been few studies on the cardiac conduction system in familial amyloidosis with polyneuropathy (FAP) (Buja et al. 1970). We have ourselves, however, in a recent report, described the marked amyloid infiltration of the atrioventricular conduction system in FAP, and concluded that this infiltration might fully explain the conduction disturbances in these cases (Eriksson et al. 1983).

Amyloid infiltration of the sinus node in other forms of amyloidosis has been documented previously (James 1966; Bharati et al. 1976; Ridolfi et al. 1977; Isokane et al. 1978; Bharati et al. 1980). Several studies (James 1966; Schroeder et al. 1975; Ridolfi et al. 1977; Isokane et al. 1978; Gray et al. 1978; Bharati et al. 1980; Olofsson et al. 1983) indicate that dysfunction of the sinus node may be more common in amyloidosis than has been thought previously. It was pointed out that the pathogenesis of dysfunction of the sinus node is not clear, but may be ascribed either to direct infiltration by amyloid or involvement of the autonomic nerves of the heart (cf. Buja et al. 1970).

ECG:s were recorded fairly shortly before death – hence the correlation with patho-anatomical findings is probably close. This correlation was how-

ever, hampered by the fact that the amyloid infilatration was extensive. In the cases where sinus node and/or atrial disease were indicated by ECG, the amyloid deposits detected microscopically were entirely compatible with the electrophysiological disturbances. However, there were also comparable amounts of amyloid in the cases which did not exhibit electrophysiological disturbances. This can be interpreted in two ways: either sufficient nodal and atrial cells were spared in the latter cases, or the disturbances of conduction were not caused by the amyloid deposits of the node but rather by another factor, e.g. involvement of autonomic nerves.

It should be pointed out that the present material consists of elderly patients, and that with advancing age, the conduction system, especially the sinoatrial node and the internodal atrial myocardium (Janse and Anderson 1974), shows a progressive and significant loss of muscle fibres and an increase of elastin, collagen, and reticular fibres (Lev 1954; Davies and Pomerance 1972; Ih and Saitoh 1982; cf. James 1961). Fatty infiltration of the sinoatrial node has also been correlated with advancing age (Lev 1954). Normal changes of senility were also found in a few cases in the present series, but these changes seemed insignificant when compared with the severity and extent of the amyloid infiltration.

Certain drugs and various pathological changes may give rise to sinoatrial disease. The latter include e.g. acute myocardial infarction, thyrotoxicosis, myocarditis and degenerative changes of the sinus node and its surroundings (see e.g. Wan et al. 1972; Evans and Shaw 1977; Bharati et al. 1980). Such pathological changes or drugs could not, however, explain the sinoatrial disease in our cases. Neither did disease of the major coronary arteries or of the sinoatrial node artery seem to be responsible for the sinoatrial disorder observed in some of our cases (cf. Davies and Pomerance 1972; Evans and Shaw 1977; Eriksson et al. 1983). Rather, our results indicate that amyloid infiltration of the sinoatrial node and the atrial myocardium accounts for the electrophysiological disturbances in these regions.

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