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Age-related histopathological changes in the cardiac conducting system in the Turkish population: an evaluation of 202 autopsy cases

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Background: *Histopathological features of the cardiac conducting system (CCS) in the Turkish population have not been investigated previously.*

Material and methods: *We examined CCS of 202 autopsy heart specimens dissected between the years 2004 and 2005 in Bursa Forensic Medicine Institution. Of the 202 cases from all age groups, 154 were males and 48 were females.*

Results: *In our cases, an increase in fibrous and adipose tissue concordant with age, indicating an age-related nature, were detected. Fibrous and fatty tissue infiltration appeared at the age of 35. Fatty infiltration started between the ages 20 and 34 years at the sinoatrial node (SAN). There was no relationship between obesity and fatty tissue infiltration in SAN and atrioventricular node (AVN). In 4 cases calcification and in 19 cases inflammation was observed. Amyloid accumulation was not present. In 7 cases myocardial infarction not involving CCS was seen. In 1 case fibroelastoma was detected.*

Conclusions: *In the Turkish population age-related fibrosis and fatty infiltration in CCS appeared at the age of 35 years and increased with age. Fatty infiltration in the SAN started at a younger age than that reported in the literature. In cases where the cause of death could not be determined, we could not detect lethal pathological features. However, we think that examination of the CCS will improve the quality of autopsy diagnosis.* (Folia Morphol 2012; 71, 3: 178–182)

Key words: heart, pathology, conduction system, forensic medicine

INTRODUCTION

All the myocytes within the heart have the capacity to conduct the cardiac impulse. A population of myocytes is specialised so as to generate the cardiac impulse and then to conduct it from the atrial to the ventricular chambers. This population has become known as the conduction system. The cardiac conduction system (CCS), consisting of the si-

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nus node, the specialised atrioventricular junction area, and the ventricular conduction tissues, is responsible for the generation and coordination of transmission of electric impulse in the heart, resulting in its rhythmic and synchronised contraction. At the end of the 19th century and in the beginning of the 20th century, it was discovered that CCS had a different histological structure compared with cardiac muscle [6, 8, 18]. Tawara's report showed us that a solitary pathway of specialised myocardium was responsible for conducting the atrial impulse to the ventricular myocardium. He described this pathway as resembling a tree, having its roots in the base of the atrial septum and its branches straddling the crest of the ventricular septum. Tawara [18] suggested that the point at which the muscle became engulfed in fibrous tissue should be taken as the boundary between the atrioventricular node (AVN) and the penetrating bundle. Within the same time period, Wenckebach et al. [20] and Thorel et al. [19] suggested that specialised tissue was present between the sinoatrial node (SAN) and AVNs; however, they were unable to demonstrate it anatomically. In subsequent years James [7] investigated atrial cells between SAN and AVNs with electron microscopy and described P cells, transitional cells, and Purkinje-like cells. As His [6] and Tawara [18]; Anderson and Ho [1] also recognised atrial transitional cells, a compact node, the penetrating bundle, and the ventricular conduction pathways as the segments of the conduction axis which can be considered to represent the specialised atrioventricular junction.

CCS is not routinely investigated in forensic medical autopsy. Therefore, CCS is specifically sampled and examined by certain authors [3, 4, 9]. Histopathological features of CCS are well defined. However, autopsy series describing age-related histopathological alterations in CCS in different populations are scarce [11, 14, 15, 17]. In this study we aimed to determine age-related histopathological alterations in CCS in the Turkish population in a large autopsy series. We also intended to show histopathological changes in CCS as a probable cause of death.

MATERIAL AND METHODS

A total of 202 hearts collected from 154 male and 48 female adult cadavers aged between 5 and 89 years were included in the present study. The subjects were from the most populated part of Turkey called Marmara, which is located in the northwest region. The autopsies were performed within 48 h of death, and during this period the bodies were kept in a cold chamber at 4°C. At autopsy the usual procedure of separating the organs was followed [13]. With the informed consent of the relatives of the deceased, the cadavers were preserved in 10% formal-saline solution. The CCSs of the hearts were cut using the method designed by Song et al. [16]. Routin dehydration and embedding in paraffin blocks were performed. Serial sections 5 μm in thickness were made (tissue slices were taken intermittently every 20th from the SAN, every 10th from the AVN), totalling about 10 slides from each case. The slides were stained with haematoxylin and eosin, and by Masson's Trichrome. In 20 randomly selected cases Congo red staining was performed. All slides were examined under light microscopy. Sections which were Congo red stained were also examined by polarised light microscopy. The amounts of fibrous tissue, fatty tissue, and inflammation were estimated by low power microscopy, i.e. estimated by the area in each section.

Statistical analysis

The data collected were analysed using SPSS 17.0 software. Descriptive statistics were calculated as the mean ± standard deviation and frequency. The Chi-square test was used to compare the categorical data. Statistical significance was defined as a p value of less than 0.05.

RESULTS

Our study included dissections of left and right atriums and left and right ventricles of hearts in 202 adult human cadavers. The mean age of the cadavers was 42.37 ± 18.1 years. Out of 202 cadavers 154 (76.2%) were males and 48 (23.8%) were females. The mean age of the males was 43.25 ± ± 17.5 years, while the mean age of the females was 39.49 ± 19.6 years ($p = 0.214$).

In 21 cases the cause of death was cardiac diseases and in 77 cases non-cardiac. In 105 cases there was no identifiable cause of death after complete autopsy was performed.

Amyloidosis was not detected in any of the Congo red stained cases. In 4 cases calcification and in 19 cases inflammation was observed. In 1 case, a 19-year-old male, fibroelastoma was detected. No tumour was located at the SAN or AVN. In 7 cases myocardial infarction was seen. In this latter group CCS involvement was not present.

Table 1. Fat infiltration in sinoatrial node (SAN) according to age groups

Age groups [years]	Fat infiltration in SAN		Total
	No	Yes	
5–19	22 (100%)	0 (0%)	22 (100%)
20–34	43 (81.1%)	10 (18.9%)	53 (100%)
35–49	23 (42.6%)	31 (57.4%)	54 (100%)
50–64	3 (7.1%)	39 (92.9%)	42 (100%)
65–89	1 (3.2%)	30 (96.8%)	31 (100%)
Total	92 (45.5%)	110 (54.5%)	202 (100%)

Chi square test: $p = 0.0001$

Table 2. Fat infiltration in atrioventricular node (AVN) according to age groups

Age groups [years]	Fat infiltration in AVN		Total
	No	Yes	
5–19	20 (90.9%)	2 (9.1%)	22 (100%)
20–34	48 (90.6%)	5 (9.4%)	53 (100%)
35–49	24 (44.4%)	30 (55.6%)	54 (100%)
50–64	3 (7.1%)	39 (92.9%0	42 (100%)
65–89	0 (0%)	31 (100%)	31 (100%)
Total	95 (47.0%)	107 (53.0%)	202 (100%)

Chi square test: $p = 0.0001$

Table 3. Fibrosis in sinoatrial node (SAN) according to age groups

Age groups [years]	Fibrosis in SAN		Total
	No	Yes	
5–19	21 (95.5%)	1 (4.5%)	22 (100%)
20–34	51 (96.2%)	2 (3.8%)	53 (100%)
35–49	26 (48.1%)	28 (51.9%)	54 (100%)
50–64	13 (31.0%)	29 (69.0%)	42 (100%)
65–89	5 (16.1%)	26 (83.9%)	31 (100%)
Total	116 (57.4%)	86 (42.6%)	202 (100%)

Chi square test: $p = 0.0001$

Table 4. Fibrosis in atrioventricular node (AVN) according to age groups

Age groups [years]	Fibrosis in AVN		Total
	No	Yes	
5–19	19 (86.4%)	3 (13.6%)	22 (100%)
20–34	46 (88.5%)	6 (11.5%)	52 (100%)
35–49	17 (31.5%)	37 (68.5%)	54 (100%)
50–64	5 (11.9%)	37 (88.1%)	42 (100%)
65–89	3 (9.4%)	29 (90.6%)	32 (100%)
Total	90 (45%)	112 (55%)	201 (100%)

Chi square test: $p = 0.0001$

There was no statistically significant difference in terms of gender, fat infiltration, fibrosis, inflammation, and calcification in either SAN, or in AVN ($p > 0.05$).

Patients were divided into five groups according to age: Group 1: 5–19 years (22 cases), Group 2: 20–34 years (53 cases), Group 3: 35–49 years (54 cases), Group 4: 5–64 years (42 cases), and Group 5: 65–89 years (31 cases). Histopathological findings were compared between these groups. As can be seen in Tables 1–4, as the age of the cases increased, the fatty tissue infiltration and fibrosis in SAN and AVN statistically significantly increased (Figs. 1, 2). There was no correlation between the age groups and the inflammation and calcification in SAN and AVNs ($p > 0.05$).

We have grouped 184 cases in whom the recordings were present, according to their body mass index (BMI) (with the metric system, the formula for BMI is weight in kilograms divided by height in metres squared) as normal, overweight and obese.

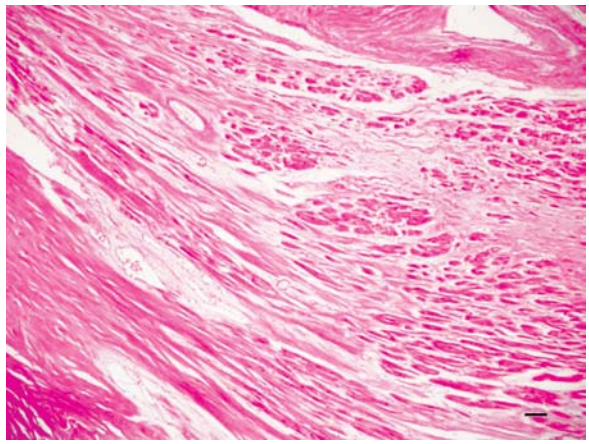

Figure 1. Fibrous tissue infiltration in sinoatrial node (scale bar: 250 μ).

In adults, BMI is interpreted using standard weight status categories that are the same for all ages and for both men and women. The standard weight status categories associated with BMI ranges for adults

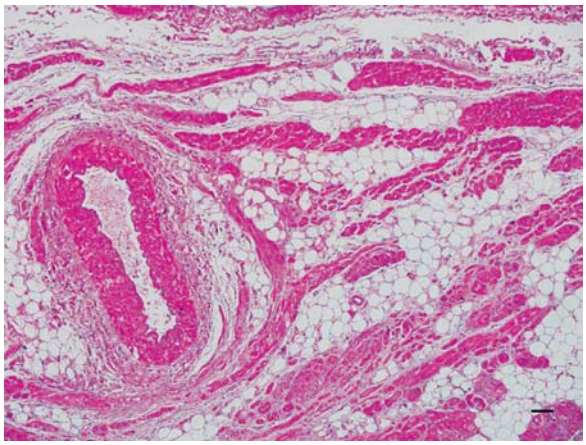

Figure 2. Fatty tissue infiltration in sinoatrial node (scale bar: 250 μ).

Table 5. The relationship between body mass index (BMI) and fatty infiltration in the sinoatrial node (SAN)

BMI	Fatty infiltration in SAN		Total
	No	Yes	
Normal	27 (61.4%)	17 (38.6%)	44 (100%)
Overweight	82 (68.9%)	37 (31.1%)	119 (100%)
Obese	17 (81.0%)	4 (19.0%)	21 (100%)
Total	126 (68.5%)	58 (31.5%)	184 (100%)

Chi-square test = 0.279

Table 6. The relationship between body mass index (BMI) and fatty infiltration in the atrioventricular node (AVN)

BMI	Fatty infiltration in AVN		Total
	No	Yes	
Normal	38 (86.4%)	6 (13.6%)	44 (100%)
Overweight	97 (81.5%)	22 (18.5%)	119 (100%)
Obese	17 (81.0%)	4 (19.0%)	21 (100%)
Total	152 (82.6%)	32 (17.4%)	184 (100%)

Chi-square test = 0.751

are: Below 18.5 is considered underweight, 18.5––24.9 is considered normal, 25.0–29.9 is considered overweight, and 30.0 and above is considered obese. In our sample, the mean BMI was 25.7 ± 4.2. We did not observe a statistically significant correlation between BMI and fatty infiltration in the SAN and AVN (Tables 5, 6).

DISCUSSION

Various studies investigating age-related alterations of CCS in different populations have been carried out. Erickson and Lev [4] observed that in AVN, infiltration of fat started at the age of 30 and became prominent after 50. In his study Lev found that in SAN fat appeared at the age of 30 and fibrous tissue became abundant by the age of 40 [9]. Buruljanowa et al. [2] showed that connective tissue increased especially in SAN after 60 years of age in their case series of 32 cadavers who died of non-cardiac causes. With a case series of 230 Chinese in their report, Song et al. [15] stated that after 40 years of age in SAN, fibrosis and fatty infiltration appeared and increased with age. They observed that in AVN, fatty change presented after 30 years of age and fibrosis presented after 60 [15]. In their study with 150 Finns, Song et al. [14] observed that in most of their cases the fibrous tissue and fatty tissue in the CCS appeared at the age of 40 and increased with aging. In their case series, fatty tissue infiltration was relatively mild. Michaud et al. [11] stated that fibrosis and fatty tissue infiltration increased with age, in their study designed in Switzerland, including 110 forensic autopsies. They showed that the evaluation of the conduction system should not be omitted in forensic medicine, especially for sudden cardiac death cases, and proposed a simple, time-efficient, low-cost technique for routine forensic autopsy. In the Turkish population, concordant with all these observations, in both SAN and AVN, fibrous tissue and fatty tissue increased in progressive age groups. In our study age-related fibrosis and fatty infiltration in CCS appeared at the age of 35 and increased with age. Fatty infiltration in SAN started at a younger age than that of reported in the literature. In the present study age was a significant predictor of fatty infiltration in CCS; however, we also wanted to find out if obesity was another predictor of fatty infiltration in CCS. After statistical analysis we did not observe that obesity was a contributing factor to fatty infiltration in CCS.

Gulino [5] described the techniques of examination of CCS in sudden cardiac death cases. They suggested that in sudden cardiac death cases, examination of the cardiac conduction system could be a useful adjunct to examination of the heart. The most common causes of sudden cardiac deaths have been reported to be arteriosclerotic narrowing of the coronary arteries, cardiomyopathy, and myocarditis, by Cohle et al. [3]. Among cases without an identifiable cause of death it was detected that the CCS had contained lesions that were considered lethal

in 11 cases: narrowing of the AVN artery by fibromuscular hyperplasia in 7 cases and AVN tumours in 4 cases. In this study the 11 cases accounted for 2.9% of the 381 cases of sudden cardiac death and 11.8% of the indeterminable cases. The authors suggested that examination of the CCS in deaths in which the gross and microscopic autopsy, history, and drug screen failed to determine a cause of death could yield a cause of death in a significant percentage of cases [3]. In our series, in 105 cases the cause of death could not be determined although complete autopsy was performed. In these cases we could not detect any lethal pathologic features.

Lumb and Shacklett [10] observed primary cardiac amyloidosis in two cases. In both cases, large masses of amyloid were seen partly destroying the AVN. Ridolfi et al. [12] studied the conduction system in autopsies of 23 cases with cardiac amyloidosis and 21 cases with abnormalities of conduction or rhythm. They observed severe fibrosis in SAN in 30% of cases with cardiac amyloidosis. We performed Congo red stain for amyloid in cases with fibrosis in SAN and AVN; however, amyloid was not detected in any of these cases.

CONCLUSIONS

Routine examination of CCS is not usually performed. It has been suggested that this procedure would be helpful in explaining the cause of death, especially in sudden death cases. We had a large group of cases (105 cases) in which the cause of death could not be determined. We expected to find out specific lethal pathologic features in at least some of these cases. Although we could not manage to observe such features, we also think that examination of the CCS will improve the quality of autopsy diagnosis.

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