Original article

Sudden Death Due to Thoracic Aortic Dissection in Young People: A Multicenter Forensic Study

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A B S T R A C T

Introduction and objectives: Thoracic aortic dissection (TAD) is infrequent in young people and its characteristics differ from those in the adult population. This study aimed to analyze the clinical and pathological characteristics of sudden death due to TAD in people aged 1 to 35 years.
Methods: Multicenter population-based study based on forensic autopsies conducted in the provinces of Biscay (1991-2016), Valencia (2000-2016), and Seville (2004-2016).
Results: We identified 35 individuals with sudden death due to TAD (80% males), with a mean age of 29 ± 5 years. The incidence was 0.09/100 000 inhabitants/y. Eighteen persons had at least 1 risk factor for TAD, and this figure increased to 29 when postmortem findings were included: congenital heart disease (n = 16), suspicion of familial TAD (n = 11), cocaine use (n = 6), and hypertension (n = 5). Twenty-four individuals, 12 with at least 1 risk factor, had prodromal symptoms, and 16 of them visited their physician, but TAD was not suspected in any of them. The most frequent symptom was chest pain (n = 12). The main autopsy findings were cystic degeneration of the media (n = 27), dilatation of the ascending aorta (n = 21), cardiac hypertrophy (n = 20), and bicuspid aortic valve (n = 14).
Conclusions: The incidence of sudden death due to TAD in young people was very low. The most frequent risk factors were congenital heart disease followed by suspicion of familial TAD and cocaine use. TAD should be included in the differential diagnosis of chest pain in young people, mainly male patients with at least 1 risk factor.

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Muerte súbita por disección de aorta torácica en jóvenes: estudio multicéntrico forense

R E S U M E N

Introducción y objetivos: La disección de la aorta torácica (DAT) es infrecuente en jóvenes y presenta características diferentes que en la población adulta. En este estudio se analizan las características clinicopatológicas de la muerte súbita por DAT de personas de 1-35 años.
Métodos: Estudio poblacional multicéntrico basado en autopsias forenses realizadas en las provincias de Vizcaya (periodo 1991-2016), Valencia (2000-2016) y Sevilla (2004-2016).
Resultados: Se recogieron 35 casos (el 80% varones), con una media de edad de 29 ± 5 años. La incidencia fue de 0,09/100.000 habitantes/año; 18 sujetos tenían algún factor de riesgo y 29, 1 o más factores de riesgo o hallazgos *post mortem* asociados con DAT: cardiopatía congénita (n = 16), sospecha de DAT familiar (n = 11), consumo de cocaína (n = 6) e hipertensión arterial (n = 5). En 24 casos, 12 con algún factor de riesgo, ya habían presentado síntomas previamente; 16 acudieron al médico, pero nunca hubo sospecha de DAT. El dolor torácico (n = 12) fue el síntoma más frecuente. Los hallazgos autópsicos principales fueron: degeneración quística de la media (n = 27), dilatación de la aorta ascendente (n = 21), cardiomegalia (n = 20) y válvula aórtica bicúspide (n = 14).
Conclusiones: La incidencia de muerte súbita por DAT fue muy baja. Los factores de riesgo más frecuentes fueron las cardiopatías congénitas, seguidas de la sospecha de DAT familiar y el consumo de cocaína. Se debería incluir la DAT en el diagnóstico diferencial del dolor torácico en jóvenes, principalmente varones, con factores de riesgo asociados.

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Abbreviations

BAV: bicuspid aortic valve
CMD: cystic medial degeneration
SCD: sudden cardiac death
SD: sudden death
TAD: thoracic aortic dissection

INTRODUCTION

Thoracic aortic dissection (TAD) is an emergency clinical situation with high mortality; hence, early diagnosis and treatment are essential for a favorable prognosis. The condition usually affects individuals older than 50 years, and the main risk factor is hypertension. It usually begins with severe chest pain of sudden onset, thus sometimes allowing the condition to be diagnosed in life.[1] Occasionally, sudden death (SD) is the first manifestation of the disease.

In young people, TAD is extremely rare,[2–5] and in persons younger than 35 years it is a rare cause of sudden cardiac death (SCD).[6–10] This age group is considered to have unique clinical and pathologic characteristics compared with adults, as well as unusual risk factors and an atypical presentation. The most important risk factors are connective tissue abnormalities and congenital cardiovascular anomalies.[2–5]

Only a few clinical series of TAD in young people have been published,[2–5] and most reports describe isolated cases retrospectively.[11–21] To our knowledge, there are no published series of SCD secondary to TAD in young people and, therefore, the characteristics of this group are poorly defined.

The purpose of our forensic study was to analyze the epidemiologic, clinical, and pathologic characteristics and the risk factors of SD due to TAD in a population aged 1 to 35 years.

METHODS

Legislation and Definition of Sudden Death

A multicenter population-based study was conducted of the forensic autopsies of victims aged 1 to 35 years who had died suddenly due to TAD.

According to the definition of SD, death occurs naturally, unexpectedly, and within 6 hours of symptom onset in persons in apparent good health carrying out their normal activities at the time of the fatal event. The definition also includes unwitnessed deaths in which the victim was last seen alive and in good health within 24 hours prior to death.[22]

Study Population. Sample Selection

Because SCD due to TAD is rare in young people, this multicenter study was designed to include the forensic services of the provinces of Biscay, Seville, and Valencia. In each province, a single forensic service performs all court-ordered autopsies for deaths occurring within their borders. The 3 forensic services created an SD registry of individuals aged 35 years or younger, and the time period analyzed covered from the date the registry was created in each province (Biscay, 1991; Valencia, 2000; Seville, 2004) up to and including 2016. The study analyzed SD registry data from the 3 forensic services for victims up to age 35 years to identify the total number of cases of SCD and the number of SCDs due of TAD. Additionally, cases of SCD due to TAD at all ages were identified. Demographic, clinical, and pathologic variables were collected for all SCD due to TAD up to age 35 years.

Autopsy Protocol

Autopsies were performed by trained forensic pathologists according to international recommendations.[22,23] We retrospectively collected information on medical history, inspection of the place of death, external examination, complete autopsy with macroscopic and microscopic examination, and toxicological analysis of blood, urine, and vitreous humor.

The diameter of the ascending aorta was measured at a distance of 1.5-2 cm from the sinotubular junction. There are no anatomic pathology criteria to define dilatation of the aorta. Postmortem studies established that the mean diameter of the ascending aorta was 2.2 cm.[24] Based on this datum and the mean age of our sample, aortic dilatation was diagnosed when the diameter was ≥ 3.5 cm (1.5-fold the normal value). Coronary atherosclerosis was considered severe when vascular lumen stenosis was $> 75\%$ and moderate between 50% and 75%.[22] The heart was considered to have an increased weight, indicative of left ventricular hypertrophy, when the value was more than 20% above the estimated weight for the victim's body weight.[25]

Epidemiological and Statistical Analysis

The incidence of SD due to TAD in persons aged 1 to 35 years subject to forensic autopsy were calculated based on 2011 population census data from the National Institute of Statistics. The population aged 1 to 35 years in Biscay was 411 220, 1 057 166 in Valencia, and 861 358 in Seville. Incidences were calculated for each sex and as a whole, and the relative risk between the sexes and the 95% confidence interval were confirmed. The numerator was the number of forensic cases of SD due to TAD in persons aged 1 to 35 years, and the denominator was the total population aged 1 to 35 years in each province, multiplied by the number of years analyzed in each province. Continuous variables are expressed as mean $\pm$ standard deviation with the percentage and range. SPSS for Windows, version 21.0, was used for the statistical analysis.

RESULTS

Demographic and Epidemiologic Data

A total of 35 cases of TAD were identified in the population aged 1 to 35 years; 80% were male, and all were Caucasian. The mean age was 29 ± 5 (19-35) years (males, 30 ± 4 years; females, 26 ± 5 years) (Figure 1). TAD accounted for 5.4% of all forensic autopsies for SCD in
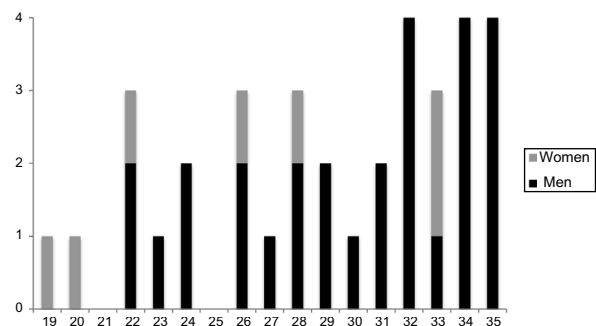

Figure 1. Sex and age at presentation of SCD due to TAD in individuals aged 1-35 years (n = 35). SCD; sudden cardiac death; TAD, thoracic aortic dissection.

Table 1

Distribution of Cases of SD Due to TAD in Individuals Aged 1-35 Years Among All Cases of SCD in Individuals Aged 1 to 35 Years and All Cases of SD Due to TAD at All Ages. Autopsy Data From the Forensic Pathology Services of the Provinces of Biscay, Valencia, and Seville

	Biscay	Valencia	Seville	Total
Period analyzed	1991-2016	2000-2016	2004-2016	
SD due to TAD, 1-35 y, n	12	16	7	35
SCD, 1-35 years, n	221	244	179	644
TAD 1-35/SCD 1-35 y, %	5.4	6.6	3.9	5.4
SD due to TAD, total, n	131	236	98	465
TAD 1-35/TAD, total, %	9.1	6.7	7.1	7.5

SCD; sudden cardiac death; SD, sudden death; TAD, thoracic aortic dissection.

young people and 7.5% of SCD due to TAD in all age brackets (Table 1). According to the forensic autopsy data, the incidence of SD due to TAD in the population aged 1 to 35 years was 0.09/100 000 inhabitants/y. The relative risk was 4-fold higher in males (95% confidence interval, 2.3-19.2).

Circumstances of Death

Most (74%) deaths were out-of-hospital, while the rest occurred during ambulance transfer or very soon after admission to the emergency room. Death usually occurred at home (60%), during a routine activity, at rest (46%), or while sleeping (11%) (Table 2).

Clinical Data

Eighteen (51%) people had a TAD-related risk factor: personal medical history (n = 10), illicit drug use (n = 5), or family history (n = 5) (Table 2 and Table 3). Before death, 24 patients had some symptoms, with chest pain being the most common (n = 12); 16 (67%) patients had visited a physician, but none suspected TAD and the diagnoses were extremely varied (Table 3).

Autopsy Findings

All dissections were Stanford type A with pericardial rupture. In no cases did dissection affect only the descending aorta (Stanford type B), although in 6 of 20 for whom this datum was known, dissection extended to the abdominal aorta. The most common macroscopic findings were dilatation of the ascending aorta (60%), increased heart weight (57%), bicuspid aortic valve (BAV) (43%), Marfan phenotype (11%), and aortic coarctation (8%). The mean heart weight was 470 ± 135 g, 32% higher than expected for body weight (355 ± 56 g). The mean diameter of the ascending aorta was 4 ± 1.3 cm, and it was > 5 cm in 4 cases. The intimal tear was most often single (86%), horizontal (57%), and at a mean distance of 2.10 cm from the sinotubular junction. In 4 cases, there were 2 tears, and in 1, there were 3 in the ascending aorta, the aortic arch, and the subclavian outflow. The histopathologic study showed cystic medial degeneration (CMD) in 27 (77%) participants. In 3 cases, no histologic study was performed on the aorta and, therefore, this datum is unknown.

The toxicologic analysis detected drugs without cardiovascular toxicity in 8 cases, usually analgesics; alcohol in 4 (2 with alcoholemia < 0.5 g/L), cocaine in 3, and cannabis in 2 (Table 4). Cocaine may have been a predisposing factor in 6 males: 5 known users (2 with positive toxicology) and 1 other case, with no known use, in which cocaine was detected in the toxicologic analysis. In these 6 cases, the histologic study revealed CMD and in 2, BAV (Table 3 and Table 4).

Table 2

Clinical Data for SD Due to TAD in Individuals Aged 1 to 35 Years (n = 35)

	n (%)
Origin of cadaver	
Out-of-hospital (cadaver release)	26 (74)
Hospital (dead on arrival or early death in emergency room, undiagnosed)	9 (26)
Place of symptom onset	
Home	21 (60)
Place of leisure	5 (14)
Work	3 (8)
Public site	2 (5)
Unknown	4 (11)
Activity	
Rest	16 (46)
Sleep	4 (11)
Physical activity	3 (8)
Unknown	12 (34)
Risk factors for TAD	18 (51)[a]
Family history	5 (14)
Medical history	10 (28)[b]
Hypertension	5
Congenital heart diseases	4
Hereditary connective system disorders	2
Severe kidney disease (dialysis)	1
Cocaine use	5 (14)
Symptoms prior to death	24 (68)
Chest pain	12
Lower back pain	3
Digestive symptoms	3
Other	6
No	9
Unknown	2

SD, sudden death; TAD, thoracic aortic dissection.
[a] Some patients had more than 1 risk factor or prior medical condition.
[b] Two cases had concomitant congenital heart disease and hypertension.

DISCUSSION

There are few hospital series of TAD in children and young people.[2–5] Although there are some isolated published reports of SD due to TAD in persons aged 35 years or younger,[11–21] our study is the first series specific to this age group. Its importance lies in the fact that the cases were out-of-hospital SDs not diagnosed antemortem, for which forensic autopsy was available. The patient population had not been included in clinical studies and provides valuable additional information to further our understanding of this rare condition. Table 5 and Table 6 compare our findings with the largest published clinical series of TAD.

Demographic and Epidemiologic Data

Although TAD is rare in young people,[2–5] there are no epidemiologic data on the incidence of this condition. In our forensic autopsy-based series, the incidence of mortality for SD due to TAD between age 1 and 35 years was very low (0.09/100 000 inhabitants/y). The percentage of TAD in large SCD series of victims aged 1 to 35 years, based on postmortem studies, ranges between 3% and 7% (Table 7),[6–10] and our study falls within this range (5.4%). The percentage of SCD due to TAD in young people compared with TAD at all age brackets was similar to that reported

Table 3
Demographic, Clinical, and Pathologic Characteristics of Cases of Sudden Death Due to TAD (n = 35)

Patient	Sex, age, y	Risk factors	Prior symptoms	Diagnosed in emergency room	Postmortem findings	Possible origin of TAD
1	M, 30	No	Chest pain	Parietal or mechanical pain	BAV, LVH, CMD, severe CA	Congenital heart disease
2	M, 27	No	Chest pain	Parietal or mechanical pain Anxiety	BAV, LVH, DAA, CMD, AA	Congenital heart disease
3	F, 33	No	Chest pain	1st consultation: mechanical pain 2nd consultation: gastroesophageal reflux	DAA	Unknown
4	M, 32	Cocaine use	Chest pain	Esophageal spasm	BAV, DAA, CMD, cocaine+	Congenital heart disease+cocaine
5	M, 26	No	Chest pain	Acute pericarditis	BAV, LVH, DAA, CMD	Congenital heart disease
6	M, 28	FH: Beals syndrome	Chest pain	Nonspecific chest pain	DAA, CMD	Suspicion of familial TAD
7	M, 32	No	Chest pain	Nonspecific chest pain	LVH, moderate CA	Unknown
8	M, 35	No	Chest pain and cough	Nonspecific chest pain	LVH, DAA, CMD	Unknown
9	M, 35	Severe kidney disease. Dialysis	Chest pain	Did not consult	BAV, LVH, DAA, severe CA, AA, CMD	Congenital heart disease
10	M, 34	Surgery for aortic stenosis in BAV	Chest pain. Restlessness	Did not consult	BAV, LVH	Congenital heart disease
11	M, 22	HTN	Chest pain	Did not consult	BAV, CoAo, LVH, DAA, CMD	Congenital heart disease+HTN
12	M, 34	No	Chest pain radiating to throat, dyspnea	Did not consult	LVH, DAA, moderate CA, CMD, cocaine+	CMD+cocaine
13	F, 22	Clubfeet, joint laxity, 37 weeks of pregnancy FH: familial hyperlaxity	Lower back pain with dyspnea	Anxiety	CMD	Suspicion of familial TAD
14	M, 34	No	Lower back pain with general malaise	Renal colic	BAV, LVH, DAA, CMD, AA	Congenital heart disease
15	M, 29	No	Lower back pain and neck pain	Did not consult	BAV, DAA, CMD	Congenital heart disease
16	F, 26	Turner syndrome (with BAV, DAA, and HT)	Abdominal pain and diarrhea. Syncope	1st consultation: acute gastroenteritis 2nd consultation: basal pneumonia	BAV, LVH, DAA, CMD	Suspicion of familial TAD+congenital heart disease+HT
17	F, 20	Turner syndrome (with BAV and DAA)	Epigastric pain and vomiting	Acute gastroenteritis	BAV, DAA. No histologic study of aorta	Suspicion of familial TAD+congenital heart disease
18	M, 33	Cocaine use	Nausea, diarrhea, posterior chest pain radiating to back. Leukocytosis	Acute gastroenteritis	LVH, DAA, CMD	CMD+cocaine
19	M, 35	FH: valve replacement surgery in 2 siblings	General malaise, dizziness, sweating, and vomiting	Did not consult	LVH, DAA, CMD	Suspicion of familial TAD
20	M, 26	HT	General malaise, dizziness	Did not consult	CoAo, LVH, DAA, AA, severe CA, CMD	Congenital heart disease+HT
21	F, 33	No	Headache	Migraine	Marfan phenotype, LVH, CMD	Suspicion of familial TAD
22	M, 35	Split palate surgery FH: aortic aneurysm and HT in father	Buccal pain, general malaise, and shivers	No urgent conditions	LVH, DAA	Suspicion of familial TAD
23	M, 24	No	Cervicobrachial pain	Did not consult	Marfan phenotype, CMD	Suspicion of familial TAD
24	M, 31	No	Sore throat	Pharyngitis	LVH, DAA, CMD	Unknown
25	M, 31	Surgery for CoAo HT	No	Did not consult	CoAo, LVH, CMD, moderate CA	Congenital heart disease+HT
26	M, 28	Cocaine use	No	Did not consult	BAV, LVH, CMD, cocaine+	Congenital heart disease+cocaine
27	F, 19	Cocaine use	No	Did not consult	CMD	CMD+cocaine
28	M, 24	Cocaine use	No	Did not consult	CMD	CMD+cocaine

Table 3 (Continued)
Demographic, Clinical, and Pathologic Characteristics of Cases of Sudden Death Due to TAD (n = 35)

Patient	Sex, age, y	Risk factors	Prior symptoms	Diagnosed in emergency room	Postmortem findings	Possible origin of TAD
29	M, 29	No	No	Did not consult	Marfan habitus, BAV, DAA, CMD	Suspicion of familial TAD + congenital heart disease
30	M, 23	No	No	Did not consult	Marfan habitus, DAA, CMD	Suspicion of familial TAD
31	M, 32	No	No	Did not consult	BAV, DAA, CMD	Congenital heart disease
32	M, 22	No	No	Did not consult	Nonspecific	Unknown
33	M, 32	No	No	Did not consult	CMD	Unknown
34	M, 34	FH: familial polycystosis	Unknown	No data	Nonspecific. No histologic study of aorta	Suspicion of familial TAD
35	F, 28	HT and hyperthyroidism	Unknown	No data	LVH, moderate CA, AA. No histologic study of aorta	HT

AA, aortic atherosclerosis; BAV, bicuspid aortic valve; CA, coronary atherosclerosis; CMD, cystic medial degeneration; CoAo, coarctation of the aorta; DAA, dilatation of the ascending aorta; F, female; FH, family history; HTN, hypertension; LVH, left ventricular hypertrophy; M, male; TAD, thoracic aortic dissection.

by Januzzi et al.[3] (7% of TAD in all persons younger than 40 years), and the proportion in participants up to age 19 years was similar to the study by Fikar and Fikar[4] (0.37% of people younger than age 21 years). As in adults,[1] TAD in youth was more common in males (75%),[1,3,4] and in our series, the relative risk was 4-fold higher for males.

Table 4
Postmortem Findings and Toxicologic Results for SD due to TAD in Individuals Aged 1 to 35 Years (n = 35)

	n (%)
Postmortem findings	
Stanford classification	
Type A	35 (100)
Marfanoid phenotype	4 (11)
Increased heart weight (left ventricular hypertrophy)	20 (57)
Dilatation of the ascending aorta	21[a] (60)
Bicuspid aortic valve	14 (43)
Aortic coarctation	3 (8)
Aortic atherosclerosis	5 (14)
Coronary atherosclerosis	
Severe	3 (8)
Moderate	4 (11)
Cystic medial degeneration[b]	27 (77)
Toxicologic results[c]	
Negative	18 (51)
Drugs	8 (23)
Paracetamol	4
Metamizole	3
Opiate analgesics	3
Benzodiazepines	2
Salicylates	1
Alcohol	4 (11)
Cocaine	3 (8)
Cannabis	2 (5)
Unknown	7 (20)

SD, sudden death; TAD, thoracic aortic dissection.
[a] In 19 cases, the diameter was ≥ 3.5 cm and in another 2, this datum was not recorded but the visual impression was evident dilatation.
[b] In 3 cases, no histologic study was performed on the aorta.
[c] In some cases, there were various toxic substances or drugs.

Risk Factors for Thoracic Aortic Dissection

At least 1 risk factor was detected in 51% of our study participants, with this figure rising to 83% when postmortem findings (marfanoid phenotype, cardiovascular abnormalities, and presence of cocaine in the toxicologic analysis) were also considered (Table 3 and Table 5). In clinical series, risk factors are present in 62%[4] to 90%[2] of youth. A review of isolated cases of SD due to TAD showed that a risk factor was found in 60% during the postmortem study; however, most were not diagnosed during the victim's lifetime (Table 5).[11–21] In the Italian series of Veneto,[9] a congenital substrate was identified in the 19 cases.

The predisposing factors were different in young people than in adults. Hypertension and atherosclerosis was present in 75% and 30% of adults, respectively.[1,3] In our series, 5 (14%) patients had been diagnosed with hypertension (3 with aortic coarctation), a level below that of the series reported by Januzzi et al.[3] (34%). No cases in our study had a history of atherosclerosis, although the autopsy revealed aortic or coronary atherosclerosis in 9 cases.

Congenital Heart Diseases

The frequency of congenital heart disease in TAD among children and young people was 46% (n = 16) in our series (Table 3), with previous studies reporting rates of 30% to 50%.[2–4] One of the most important was BAV,[26,27] observed in the autopsy of 14 (43%) cases. In BAV, the risk of dissection is 5- to 18-fold higher than in the case of the tricuspid aortic valve.[26] Another anomaly associated with TAD was aortic coarctation,[27] detected in our series in 3 cases with a history of hypertension. Cardiac surgery on the aortic valve, a prior condition reported in 1 case, was also related to a higher risk of TAD.[3]

Hereditary Disorders

Hereditary connective system disorder-related TAD usually occurs in young people, and Marfan syndrome is the best known.[27] In clinical series, its frequency is between 40% and 50%.[2,4]

In our series, 11 (31%) cases had a possible predisposing genetic substrate (Table 3). In 4 individuals, the autopsy reported marfanoid phenotype, none diagnosed in life. A review of the 11 isolated cases of SD due to TAD with a postmortem study (Table 5 and Table 6[11–21]) found only 1 case.[16] This lower frequency of Marfan syndrome in forensic series may be due to greater clinical suspicion, thus making it more likely for the

Table 5

Main Clinical Characteristics of TAD Series in Individuals Younger Than 35 Years

Reference	Zalzstein et al.[2]	Januzzi et al.[3]	Fikar and Fikar[4]	Deshpande et al.[5]	Isolated cases of sudden death[11–21]	Morentin Campillo, 2018[a]
Origin	Clinical	Clinical (IRAD)	Clinical (SPARCS)	Clinical	Clinical and forensic autopsies	Forensic autopsies
DAT, no.	13	68	45	12	11	35
Nontraumatic TAD, no.	10	68	26	12	11	35
Type of TAD, no.						
A	8	46	NK	NK	6	29[b]
B	2	22	NK	NK	5	
Age, y, mean (range)	≤ 25 12.1 (0-25)	≤ 40 30.7 ± 6.6	≤ 21 18.4 ± 1.93 (15-21)	≤ 3.5 1 mo	≤ 35 22.45 (15-33)	≤ 35 28.7 ± 4.8 (19-35)
Males, %	54	76	82	NK	64	80
Risk factors, %[c]						
No	10	NK	38	0	45	17
Marfan syndrome	40	50	42	0	9	11
Hereditary TAD (not Marfan)	0	NK	NK	33	9	20
Congenital heart diseases	50	31	31	67	18	46
Hypertension	NK	34	12	0	18	14
Cocaine	0	0	0	0	0	17
Symptoms at presentation, %						
Precordial pain	40	100	NK	0	45	34
Death	38	22	13	0	100	100

IRAD, International Registry of Acute Aortic Dissection; NK, not known; SPARCS, Statewide Planning and Research Cooperative System (New York State Department of Health patient database); TAD, thoracic aortic dissection.

[a] Present article.
[b] In 6 cases, this datum was not known.
[c] Cases caused by trauma were excluded; sudden death series include both clinical patients and autopsies.

condition to be diagnosed during the person's lifetime. In addition, 2 patients had been diagnosed with Turner syndrome. Because TAD is associated with BAV, dilatation of the ascending aorta, and aortic coarctation, it is 6-fold more common in Turner syndrome than in the general population and tends to occur in childhood and adolescence. This complication accounted for 8% of deaths in Turner syndrome.[28]

Another 5 participants with a family history indicating a genetic basis could be included (Table 3): 1 with a family history of Beals syndrome (case 6), another suspected to have Ehlers-Danlos syndrome (case 13), and a third suspected to have Loeys-Dietz syndrome (case 22).[27] The fourth patient had a family history of autosomal dominant polycystic kidney disease (case 34). Only a few cases of this association have been described in

Table 6

Main Characteristics of Isolated Cases of SD Due to TAD in Individuals Younger Than 35 Years (Autopsy-based Studies)

Reference	Age, y	Stanford classification	Prior symptoms	Presumptive diagnosis	Progress	Risk factors	Postmortem findings
Fikar et al.[11]	15	B	Sudden pain in back and left abdomen	Nonspecific pain	2 h	No	No
Hogan[12]	27	A	SD		0	Connective tissue disease SD mother, TAD	Fibrillin disease
Ngan et al.[13]	17	B	Sudden pain in back and left abdomen	Retroperitoneal hematoma	36 h[a]	No	No
Mimasaka et al.[14]	24	A	Sore throat	Laryngopharyngitis	24 h[b]	No	Turner phenotype, aortic coarctation
Lynch et al.[15]	17	A	Chest and abdominal pain		0	No	Aortic coarctation
Klintschar et al.[16]	31	A	SD		0	SD father, TAD	Marfan syndrome[c]
Kim and Smith[17]	18	B	Chest and back pain	PTE	Hours (not specified)	No	No
Pachar et al.[18]	18	B	SD		0	No	No
Pineault et al.[19]	33	A	Chest pain	Pericarditis	5 d[b]	HTN, LVH, aortic root dilatation	LVH, dilatation of ascending aorta
Srettabunjong[20]	32	A	Chest and back pain	Preeclampsia (37 weeks of pregnancy)	7 d[b]	HTN, receiving therapy	Aortic atherosclerosis
Hajimaghsoudi et al.[21]	15	B	Chest and back pain	TAD on CT	Hours (not specified)	No	No

CT, computed tomography; HT, hypertension, LVH, left ventricular hypertrophy; PTE, pulmonary thromboembolism; SD, sudden death; TAD, thoracic aortic dissection.

[a] Surgery.
[b] Hospitalization.
[c] Postmortem genetic study.

Table 7

Demographic and Epidemiologic Data in the Main SCD Series Among Individuals Aged 1 to 35 years Compared With the Current Study

Reference	Region/country	Education, y	Population aged 1-35 y[a]	Population[a]	SCD cases at age 1 to 35 y, no.	TAD cases at age 1 to 35 y, no.	TAD/SCD at age 1 to 35 y, %
Doolan et al.[6]	Australia	1994-2002	NK	2	193	6	3.0
Puranik et al.[7,b]	Australia	1995-2004	NK	2.5	241	13	5.4
Winkel et al.[8]	Denmark	2000-2006	2.38	5.38	314	21	6.7
Thiene et al.[9]	Veneto (Italy)	1980-2013	1.387[c]	4.380	650	19	3.0
Bagnall et al.[10]	Australia and New Zealand	2010-2012	12.59	26.74	490	19	4.0
Morentin Campillo, 2018[d]	Biscay, Seville, and Valencia (Spain)	1991, 2004, 2000-2016	2.329	5.650	644	35	5.4

SCD; sudden cardiac death; TAD, thoracic aortic dissection.

[a] Millions of inhabitants.

[b] In this series, the age range was 5 to 35 years.

[c] Youth population (age 12-35 years).

[d] Present article.

individuals younger than age 35 years.[29] The fifth case had a family history of valve disease, and the postmortem study revealed dilatation of the ascending aorta and CMD (case 19).

The high frequency of hereditary risk factors highlights the importance of identifying patients with underlying genetic mutations.[30] A recent article has described the characteristics of 4 cases with their molecular genetic basis.[5] During autopsy, it is recommended that samples be taken (blood in EDTA at −80 °C) for genetic studies. A family study is also recommended in the current scientific guidelines.[22] By including multidisciplinary studies when investigating SCD, the number of TAD cases of unknown origin are expected to drop due to family cardiologic assessment and due to advances in cardiovascular genetics.

Substance Abuse

Cocaine use is associated with numerous cardiovascular complications and with SCD.[31] Recent cocaine use leads to an increased risk of SCD of up to 4-fold[32] among young people and, although rare, is another significant risk factor for TAD.[33] In a study by Hsue et al.,[33] 14 of 38 cases of TAD were associated with recent cocaine use, particularly in youth. In our study, cocaine was a risk factor in 6 (17%) participants, a much higher frequency than that reported in surveys on cocaine use among the general population[34]; 2 of the 6 cases had BAV; however, the presence of CMD in all of them was more relevant. These data indicate that cocaine may have an effect on a weakened aortic wall and increase the risk of dissection. The frequency of cannabis use was 8%, an expected level in view of cannabis use and the long mean half-life of the Spanish population.[34] The relatively high presence of analgesic drugs in the toxicologic analysis is not surprising, given the prevalence of pain symptoms prior to death.

Clinical Presentation

Early diagnosis of TAD is clearly important in view of its high immediate mortality. Severe chest pain of rapid onset is the most common symptom of presentation[1,3]; 12 (34%) victims had this symptom and 8 consulted a physician, although none suspected TAD even though risk factors were recorded in the history of 2. From a medical and legal point of view, this diagnostic error could lead to claims being filed for medical malpractice. Likewise, 3 of the 4 individuals with chest pain who did not consult a physician had risk factors. Failure to suspect this condition in persons with chest pain and with risk factors for TAD when they visit the emergency room and the failure of some persons to consult the emergency room are certainly an important health issue.

Our data indicate that TAD should be included in the differential diagnosis of young patients with precordial pain and a concomitant illness, particularly in the presence of hypertension or left ventricular hypertrophy on electrocardiography.

On many occasions, the course of TAD is characterized by a nonspecific picture with atypical symptoms (34% had symptoms other than chest pain before death) or a cataclysmic onset (26% had no previous symptoms). In both situations, a high degree of clinical suspicion is needed and, consequently, diagnosis is extremely difficult. Roberts et al.[35] suspected that 23% cases of TAD are not clinically diagnosed (due to the low rate of clinical autopsies), a supposition that is also supported by some forensic series.[36]

Anatomic Pathology

Stanford type A dissections, detected in all our cases, also predominate at these ages and, as in the case of adults, onset consists of SD more often than in the case of type B.[37] Conversely, Januzzi et al.[3] reported that up to 32% of TAD in young people only affected the descending aorta. This difference could be explained by the type of sample (forensic vs hospital).

Increased heart weight indicating left ventricular hypertrophy was detected in 57% of cases, a very high figure for a young population. The condition appears to have several causes, among them congenital heart disease (mainly BAV and, to a lesser extent, aortic coarctation), hypertension, obesity, severe kidney disease, and cocaine use.

Some patients with TAD have been reported to have dilatation of the ascending aorta, which showed a high prevalence (60%) in our study but which had only been recorded as medical history for 1 patient diagnosed with Turner syndrome. This finding should be interpreted with caution from the clinical standpoint because there is no adequate correlation between postmortem values for aorta diameter and values obtained from living patients by imaging techniques.

In 27 (77%) cases, we observed CMD, a characteristic but poorly specific sign of various hereditary connective tissue disorders. This term has been used in a confusing manner, and recent efforts have unified the criteria used to recognize characteristic histopathologic patterns for certain genetic aortic syndromes, for the purpose of distinguishing between the various etiologies.[38]

Limitations

Due to the retrospective nature of the study, in the oldest autopsies the aorta was not measured precisely; hence, the grade

of dilatation might not have been accurately established. Furthermore, there is no adequate correlation between postmortem values for aorta diameter and values obtained from living patients by imaging techniques. Although all dissections were Stanford type A, in some cases we could not rule out extension of the dissection to the descending aorta. Last, the study analyzed a small number of fatal cases of TAD in a series of forensic autopsies; however, our results appear to confirm and to add new information to reports from previous clinical studies about this rare condition. Therefore, these data are useful from the clinical standpoint and can be cautiously extrapolated to the general population.

CONCLUSIONS

The incidence of SCD due to TAD in individuals younger than 35 years is very low, and the population at greatest risk are young males. The most common risk factor is congenital heart disease, a condition often not diagnosed during the victim's lifetime. Familial TAD syndrome was suspected in almost one third of cases. Another significant risk factor is cocaine use. In one third of cases, SD was preceded by symptoms of chest pain. Consequently, SD should be included among the possible diagnoses of severe precordial pain once an ischemic origin has been excluded. On occasions, TAD can be diagnosed, although a high degree of clinical suspicion is needed, particularly among younger patients. The inclusion of forensic sources in acute aortic disease registries, such as the RESA (Spanish Registry of Acute Aortic Syndrome),[1] would provide useful data to supplement hospital data.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

– TAD generally affects people older than 50 years. In young people, this is a rare cause of SCD. Few series have investigated the problem of TAD in patients younger than 35 years. This age bracket has distinct clinical and pathologic characteristics from adults, with unusual risk factors and atypical presentation.

WHAT DOES THIS STUDY ADD?

– The incidence of SCD due to TAD up to age 35 years is very low, and the condition mainly affects young males. The most important risk factor is congenital heart disease, followed by familial TADs and cocaine use. The differential diagnosis of chest pain in young people should include TAD, particularly when there are risk factors. Forensic study can more clearly define the characteristics of TAD and be useful to identify the index case and to enhance subsequent cardiologic and genetic studies of family members.

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