Association of Antemortem Central Nervous System Symptoms and Location of Aortic Dissections; A Retrospective Study from 2001-2014

Wendy MacKerricher, Robert R. Klein, David C. Winston

ABSTRACT

Aortic dissections (AD) are a frequent cause of sudden death and are typically associated with chest, back, and/or abdominal pain. Several cases of AD with neurologic presenting symptoms, such as paresthesia, headache, and seizures were noted at the Pima County Office of the Medical Examiner (PCOME) in Tucson, Arizona. Our aim was to compare the location of AD with central nervous system (CNS) versus classic symptoms. Retrospective data were collected from the archives at the PCOME from 2001-2014. There were 61 natural death cases involving the aorta with known antemortem symptoms; 43 cases of AD with classic (non-CNS) symptoms and 18 cases with CNS symptoms. The cases were classified based on DeBakey and Stanford classification systems. Patients with CNS symptoms had a greater proportion of DeBakey type II dissections (44%) than without CNS symptoms (16%). This association was statistically significant ($p = 0.0337$, chi-square test). Seventeen percent of cases with CNS symptoms had AD involving the carotid arteries, and involvement of the carotid arteries was significantly associated with CNS symptoms ($p = 0.0227$, Fisher's exact test). There were a higher percentage of females with CNS symptoms (44%), than without CNS symptoms (23%). Our findings suggest a need for a higher index of suspicion and further investigation of cases with neurologic symptoms, focusing particularly on the aortic arch and its branches. *Acad Forensic Pathol.* 2016 6(3): 517-523

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INTRODUCTION

The first aortic dissection (AD) was documented in King George II of Great Britain in 1760, who died from pericardial tamponade due to an ascending AD (1). The term aortic dissection, however, was not coined until the early 1800's by René Laennec, a French physician, who notably invented the stethoscope (1). In 1954, the first successful dissecting aortic aneurysm repair was performed by Dr. Michael DeBakey and his team, who also created one of the most common classification systems for ADs (1). Ironically, DeBakey himself later suffered from an acute AD (1).

Aortic dissections are a rare but serious condition that primarily occur in older men. The incidence of ADs is 6000-10 000 cases per year (2, 3), with a prevalence of 3-4% in those over 65 years of age (4). The International Registry of Acute AD (IRAD) was established in 1996 and consists of 30 large referral centers in 11 different countries. This substantial database assesses the etiology, presentation, clinical features, treatment, and outcomes of patients with acute ADs (5). Due to the size of this database, many epidemiological and interesting facts have been discovered, including a predisposition for ADs to present in the morning (six o'clock in the morning to noon) and in the wintertime (5). Some theories suggest this is due to rhythmic variation in sympathovagal balance (6).

The risk factors for ADs are divided into two broad categories. The first category includes conditions that lead to medial degeneration: Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome (type IV), inflammatory diseases of the aorta, Turner syndrome, bicuspid aortic valve, familial thoracic aortic aneurysm, and dissection syndrome (4, 7, 8). Patients with Marfan syndrome (incidence of one in 3000 - 5000), caused by a mutation in one of the genes coding for fibrillin-1, are the largest group of genetically predisposed individuals, accounting for approximately 10% of all cases of ADs (4, 7). Those with Marfan syndrome have a 50% risk of AD in their lifetime (9). The second category involves conditions that lead to increased aortic wall stress, such as hypertension, physical trauma, and smoking (7).

The Stanford classification system places dissections into two categories based on involvement of the ascending aorta: type A involves the ascending aorta, and can extend into the descending aorta; whereas type B is confined to the descending aorta. The DeBakey classification system splits AD into three groups: type I originates in the ascending aorta, but can extend into the aortic arch and descending aorta; type II is confined to the ascending aorta only; and type III is limited to the descending aorta.

Aortic dissections are often asymptomatic, with only 5% of people reporting symptoms before an acute event, while for the remaining 95% the first symptomatic presentation often results in death (9). The IRAD found that of those who described symptoms, 79% had chest pain and 90% described the pain to be "severe" or the "worst ever" experienced (5). Due to the generalized symptom of chest pain and difficulty in diagnosis, ADs are missed in 16-38% of emergency department presentations (10, 11). The delay in diagnosis can result in extremely detrimental outcomes, including death. One study found the mortality of untreated type A dissections increases by 1-2% every hour in the first 48 hours, reaching 50% mortality by day three, and 80% mortality by two weeks (1). Type B dissections have a better prognosis, with a mortality of 10% at 30 days for low risk patients and 70% for those at high risk (1).

While the findings of the sequelae of AD at autopsy (hemothoraces, hemoperitoneum, hemopericardium) almost always cinch the cause of death, often the presenting symptoms are overlooked. The limited publications documenting neurologic symptoms in ADs have reported that neurological deficits can be found in 17-40% of all patients with ADs (3). Our aim was to identify and compare the location of ADs in patients presenting with central nervous system (CNS) versus classic symptoms. The Pima County Office of the Medical Examiner (PCOME) in Tucson, Arizona had two cases with CNS symptoms (paresthesia and altered mental status) within a two-week period, which prompted this study.

METHODS

Retrospective data were collected from the archives at the PCOME between January 2001 and December 2014. Information was gathered from death investigation reports, emergency services notes, hospital notes, and autopsy reports. The initial search included all natural deaths that had the terms “aorta,” “dissection,” “hemopericardium,” “hemothorax,” or “hemoperitoneum,” or some variant in the cause of death statement. Those without a dissection, witnesses to relay antemortem symptoms, or autopsy were removed. In the remaining deaths, data were collected to include age, race, sex, symptoms, location of dissection, involvement of carotid arteries, heart weight, left ventricle thickness, comorbidities including other heart diseases, and body mass index (BMI). The cases were classified based on location according to the DeBakey and Stanford classification systems for ADs.

All statistical tests and analyses were performed using JMP Pro Statistical Discovery software version 11.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The original broad search criteria yielded 185 cases. Of these, 124 cases were eliminated with either non-dissection causes of death including aortic stenosis, aortic valve repair, endocarditis, aortitis, and myocar-

dial infarction, or did not have documented antemortem symptoms. The remaining 61 cases of ADs were confirmed to be natural deaths and meeting our criteria of having known antemortem symptoms and an autopsy. Of these 61 deaths, Stanford type A dissections (n=39) accounted for 64%, with an average age of 54.4 years. Stanford type B (n=22) were found in 36%, with an average age of 65.1 years. Using the DeBakey classification system, ADs in this study were: type I = 39% total (71% male, 29% female) with an average age of 50.9 years; type II = 25% total (73% male, 27% female) with an average age of 58.8 years; and type III = 36% total (68% male, 32% female) with an average age of 65.7 years.

Of the 61 cases, 43 had classic (chest, back and/or abdominal pain) symptoms and 18 had CNS symptoms. Within the non-CNS or more classic symptoms, chest pain (n=17) was the most common finding, followed by abdominal pain (n=13), nonspecific pain (n=10), and back pain (n=9). The most common symptoms found among the CNS group included: paresthesia/pain in extremities (n=6), dizziness (n=5), headache (n=4), confusion/altered mental status (AMS) (n=4), back pain (n=3), syncope (n=2), and abdominal pain (n=1). Except for syncope and back pain, all these symptoms had a statistically significant association with either the presence or absence of CNS symptoms (**Table 1**).

Table 1: Symptoms

Central Nervous System				Classic			
Symptom	Number	Percent	p value*	Symptom	Number	Percent	p value*
Paresthesia	6	29%	0.0003	Chest pain	17	35%	0.0012
Dizziness	5	24%	0.0014	Abdominal pain	13	27%	0.0469
Headache	4	19%	0.0059	Nonspecific pain	10	20%	0.0261
Confusion /Altered mental status	4	19%	0.0059	Back pain	9	18%	0.6989
Back pain	3	17%	0.6989				
Syncope	2	9%	0.0836				
Abdominal pain	1	6%	0.0469				

* Fisher's exact test

Documentation of where death occurred was available for all cases and were separated into three groups: death at home, death enroute or upon arrival to hospital, and death after several hours of hospital stay. It was found that more patients exhibiting classic symptoms (30%) survived in hospital than those with CNS symptoms (22%). Death at home accounted for the majority of cases in both groups, with classic symptoms accounting for 54% and CNS symptoms, 39% (**Table 2**).

There was a higher percentage of females with CNS symptoms (44%) than with classic symptoms (23%). The median age was similar in both categories: CNS symptoms at 58.5 years and classic symptoms at

57.3 years. Ninety-four percent of patients with CNS symptoms were Caucasian compared to 65% of patients with classic symptoms. Patients with CNS symptoms had a greater proportion of Debakey type II dissections (44%) than those without CNS symptoms (16%). This association was statistically significant ($p = 0.0337$, chi-square test). Seventeen percent of cases with CNS symptoms had dissections involving the carotid arteries, and involvement of the carotid arteries was significantly associated with CNS symptoms ($p = 0.0227$, Fisher's exact test). Of the cases involving the carotid arteries, 66% were male and had an average age of 57.7 years. Symptoms included confusion/AMS ($n=2$), syncope ($n=1$), and paresthesia/pain in extremities ($n=1$). Hemopericardium was present in 67% of cases with CNS symptoms, with an average volume of 271 mL versus 47% of cases with classic symptoms, with an average volume of 388 mL. Patients with classic symptoms had larger heart sizes and thicker left ventricular walls: 547 g and 1.62 cm versus 470 g and 1.46 cm, respectively as compared to those with CNS symptoms (**Table 3**).

Aortic aneurysms (any location) were associated with an aortic dissection in 36% of all cases. Twenty-eight percent of CNS symptom patients had an associated aortic aneurysm versus 40% of classic symptom patients; however, the presence of an aortic aneurysm was not found to be statistically significant. Body mass index (weight in kg/height in m^2) of patients with CNS symptoms was more likely to be normal compared to those with classic symptoms. The classification scheme of normal (BMI <25), overweight (BMI=25-30), obese (BMI=30-40), and morbidly obese (BMI >40) was utilized. Fifty-five percent of patients with CNS symptoms had a normal BMI, 28% were overweight, and 17% were obese. Thirty percent of classic symptom patients had a normal BMI, while 35% were overweight, 30% were obese, and 5% were morbidly obese.

There was an overall higher incidence of hypertension in overweight and obese patients (97%) than those with a normal BMI (82%). Hypertension was defined as having antemortem clinical documentation of hypertension or increased heart weight at autopsy (12).

Table 2: Location of Death

Disposition	Central Nervous System		Classic	
	Number	Percent	Number	Percent
Died at home	7	39%	23	54%
Died enroute or upon arrival to hospital	7	39%	7	16%
Died after several hours in hospital	4	22%	13	30%

Table 3: Central Nervous System vs. Classic Symptoms Comparisons

	Central Nervous System	Classic
Total Number	18	43
Female (% total)	44%	23%
Caucasian (% total)	94%	65%
Age (mean)	58.5 years	57.3 years
Hemopericardium	67%	47%
Hemopericardium volume	271 mL	388 mL
Heart weight	470 g	547 g
Left ventricle thickness	1.46 cm	1.62 cm
Hypertension	89%	93%
Body mass index (kg/ m^2)	24.9	28.2
Debakey type II	44%	16%
Stanford type A	78%	58%

When classified based on CNS symptoms there was a higher incidence of hypertension in the normal (90%) than in the overweight group (80%), in direct opposition to those with classic symptoms, who showed a higher proportion of hypertension in the overweight (100%) than normal group (75%).

A diagnostic decision tree was produced using a partition model. A partition model recursively partitions data using classic statistical tests in order to classify a case. In this context, a decision tree to predict patients with CNS symptoms was produced. This tree included four branch points or key questions used to predict CNS symptoms: Chest pain, nonspecific symptoms, Debakey type II dissection and BMI ≥ 26.6 . When

these four questions are answered, all but five cases (89%) were classified correctly (**Figure 1**).

Only one patient had a connective tissue disease (Ehlers-Danlos syndrome).

DISCUSSION

Aortic dissections are a relatively common cause of sudden death within the medical examiner's office. Classically thoracic and abdominal ADs present with abrupt, severe chest, back, and/or abdominal pain, followed by sudden death. Our findings are consistent with those found in the literature that Stanford type A dissections account for two-thirds of cases versus

Figure 1: Decision tree (central nervous system symptoms – blue; classic symptoms – red). Y = Yes; N = No; BMI = Body mass index; G² = Likelihood-ratio chi-square.

type B representing one-third of ADs; our findings are type A (64%) vs. type B (36%) (3, 5). This finding holds true for the DeBakey classification system: type I and II represents two-thirds of cases, and type III one-third; compared to our results of type I/II (64%) versus type III (36%).

There are relatively few journal articles which address the association between neurological symptoms and ADs. One paper describes a variety of neurological deficits that were found in 17-40% of all ADs studied (3). Syncope has been reported in up to 17% of patients presenting with type A dissections (13). Mortality of those with syncope was found to be higher (34%) than those who did not have syncope (24%) (14). Our study found syncope in only 11% of patients ($n=2$) with CNS symptoms. Acute neurological deficits or coma were found in 30% of people with type A dissections, which is slightly less than our reported results of 36% (13). The median age is similar between both the CNS and classic groups: 57.3 years and 58.5 years, respectively.

A greater proportion of decedents with CNS symptoms had an AD involving the ascending aorta (Stanford type A, 78%; DeBakey type I/II, 83%) than those with classic symptoms (58%; 56%). A significant relationship was found between those who had CNS symptoms and DeBakey type II dissections ($p = 0.0337$, chi-square test). These findings may be due to alterations in blood flow to the brain and/or spinal cord causing acute neurological symptoms. We found that CNS symptoms were associated with dissections involving the carotid arteries ($p = 0.0227$, Fisher's exact test). Seventeen percent of our cases with CNS symptoms had involvement of the carotid arteries. Previous studies noted that focal neurological findings may be seen in patients with a dissection that extends to the spinal or carotid arteries; however, the percentage of patients was not reported (3). One retrospective study found that 94% of patients without neurological symptoms experienced pain, while only 66% of patients with neurological symptoms had chest pain (15). Interestingly, none of our patients with CNS symptoms had a history of chest pain.

Symptoms were documented in all cases, as well as location of death/hospital stay prior to death where applicable. The majority of decedents within the CNS and classic symptom groups died at home or enroute/on arrival to the hospital. Thirty percent of those with classic symptoms died after several hours in hospital, as opposed to 22% of CNS symptoms.

One report found that altered mental status was more common with pericardial tamponade (14). At autopsy, we were unable to determine if the decedents experienced pericardial tamponade; however, hemopericardium was found in 67% of cases with CNS symptoms (average volume of 271 mL), compared to 47% of cases with classic symptoms (average volume 388 mL). All patients with altered mental status were found to have a hemopericardium.

The male to female ratio of ADs has generally been noted in the literature as 3:1 (3, 6); however, more recent studies have found the incidence may in fact be closer to the findings in our study of 2.4:1 (16, 17). We found there is an increased frequency of females with CNS symptoms (44%; ratio 1.25:1) than without CNS symptoms (23%; ratio 3.3:1).

An interesting finding within our patient population is the high prevalence of Caucasians with CNS symptoms (94%) versus non-CNS symptoms (64%). This may be due to a familial link or genetic predisposition that is not yet elucidated, thought to be in up to 20% of patients with sporadic ADs (4, 9). Body mass index, heart size, left ventricular thickness, and hypertension were found to be higher in patients with classic symptoms. Within the classic symptom group hypertension was more commonly seen in patients who were overweight or obese, as opposed to the CNS symptom group where a higher proportion of those with hypertension had a normal BMI.

CONCLUSION

Antemortem CNS symptoms are probably more common than most forensic pathologists would predict in patients who die from AD. The ADs in these patients

are most likely to be proximal (Stanford A or DeBakey I/II). Our findings show that AD should be on the differential diagnosis when presented with a decedent who exhibited antemortem neurological symptoms.

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