Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 60, No. 5, 2012
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2011.12.052

Aggressive Cardiovascular Phenotype of Aneurysms-Osteoarthritis Syndrome Caused by Pathogenic *SMAD3* Variants

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Objectives The purpose of this study was describe the cardiovascular phenotype of the aneurysms-osteoarthritis syndrome (AOS) and to provide clinical recommendations.

Background AOS, caused by pathogenic *SMAD3* variants, is a recently described autosomal dominant syndrome characterized by aneurysms and arterial tortuosity in combination with osteoarthritis.

Methods AOS patients in participating centers underwent extensive cardiovascular evaluation, including imaging, arterial stiffness measurements, and biochemical studies.

Results We included 44 AOS patients from 7 families with pathogenic *SMAD3* variants (mean age: 42 ± 17 years). In 71%, an aortic root aneurysm was found. In 33%, aneurysms in other arteries in the thorax and abdomen were diagnosed, and in 48%, arterial tortuosity was diagnosed. In 16 patients, cerebrovascular imaging was performed, and cerebrovascular abnormalities were detected in 56% of them. Fifteen deaths occurred at a mean age of 54 ± 15 years. The main cause of death was aortic dissection (9 of 15; 60%), which occurred at mildly increased aortic diameters (range: 40 to 63 mm). Furthermore, cardiac abnormalities were diagnosed, such as congenital heart defects (6%), mitral valve abnormalities (51%), left ventricular hypertrophy (19%), and atrial fibrillation (22%). N-terminal brain natriuretic peptide (NT-proBNP) was significantly higher in AOS patients compared with matched controls ($p < 0.001$). Aortic pulse wave velocity was high-normal (9.2 ± 2.2 m/s), indicating increased aortic stiffness, which strongly correlated with NT-proBNP ($r = 0.731$, $p = 0.005$).

Conclusions AOS predisposes patients to aggressive and widespread cardiovascular disease and is associated with high mortality. Dissections can occur at relatively mildly increased aortic diameters; therefore, early elective repair of the ascending aorta should be considered. Moreover, cerebrovascular abnormalities were encountered in most patients. (J Am Coll Cardiol 2012;60:397–403) © 2012 by the American College of Cardiology Foundation

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Manuscript received September 6, 2011; revised manuscript received December 5, 2011, accepted December 18, 2011.

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Abbreviations and Acronyms

AF = atrial fibrillation

AOS = aneurysms-osteoarthritis syndrome

aPWV = aortic pulse wave velocity

CTA = computed tomography angiography

LDS = Loeys-Dietz syndrome

MFS = Marfan syndrome

NT-proBNP = N-terminal brain natriuretic peptide

TAAD = thoracic aortic aneurysms and dissections

TGF = transforming growth factor

TTE = transthoracic echocardiography

Aortic aneurysms and dissections were ranked as the nineteenth most common cause of death in the United States in 2007 (1). The true incidence is probably much higher, because many aortic aneurysms are silent. Thoracic aortic aneurysms and dissections (TAADs) often are found in the context of genetic syndromes, such as Marfan syndrome (MFS) and Loeys-Dietz syndrome (LDS), but also are associated with bicuspid aortic valves (2–4). MFS is one of the most common hereditable connective tissue disorders, with abnormalities predominantly in the skeletal, ocular, pulmonary, and cardiovascular systems (2). LDS shows some similarities with MFS, but exhibits widespread arterial aneurysms and tortuosity (3).

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Recently, our group found that pathogenic *SMAD3* variants cause aneurysms-osteoarthritis syndrome (AOS) (5). AOS is inherited as an autosomal dominant disorder and is found to be responsible for 2% of familial TAADs (5,6). Aneurysms, dissections, and tortuosity throughout the arterial tree are the main cardiovascular features (5). In addition, early-onset osteoarthritis is present in almost all patients and often is the first reason to seek medical advice (5). Mild craniofacial abnormalities, such as hypertelorism and bifid uvula, also are associated with AOS (5). Furthermore, umbilical or inguinal hernias, or both; varices; velvety skin; and striae are common findings (5). The purpose of this study was to describe the cardiovascular consequences of AOS and to provide clinical recommendations.

Methods

From 2009 onward, all AOS patients with a pathogenic *SMAD3* variant in participating centers were included in this ongoing cohort study. Genetic identification methods have been described previously (5). Patients underwent comprehensive clinical evaluation, including risk factor assessment, physical examination, biochemical measurements, 12-lead electrocardiography, transthoracic echocardiography (TTE), and computed tomography angiography (CTA) of the thorax and abdomen. For logistical reasons, not all examinations could be performed in every patient. In a subset of patients, CTA of the cerebral vessels and arterial stiffness measurements also were performed. These methods are described extensively in the Online Appendix. Patients were monitored for occurrence of cardiovascular events, especially dissection or mortality. Autopsy was requested in case of death and was performed when possible. Biochemical and arterial stiffness measurements were compared 1-to-1 with age-, sex-, and smoking status-matched controls. Apparently healthy controls were recruited among hospital personnel and their acquaintances and underwent only biochemical and arterial stiffness measurements and smoking status assessment. The study was approved by the Institutional Review Board and Ethical Committee of the Erasmus Medical Center in Rotterdam. Written informed consent was obtained from each patient.

Data analysis. SPSS software version 15.0 (SPSS, Inc., Chicago, Illinois) was used for the statistical analyses. A p value of <0.05 was considered statistically significant. The 1-sample Kolmogorov-Smirnov test and histograms were used to check normality. Normally distributed continuous data are presented as mean ± SD, and categorical variables are presented as frequency (n) and percentages. Non-normal distributed data are presented as median with interquartile range (25th and 75th percentiles). For comparison between the control and patient groups, a Student *t* test taking into account the 1-to-1 pairing or the signed-rank Wilcoxon test was used. Biochemical measurements also were compared with reference values from the clinical chemical laboratory of the Erasmus Medical Center in Rotterdam. For correlation analysis, the Pearson r correlation coefficient and Spearman correlation test were used.

Results

We here describe the cardiovascular features of 44 AOS patients from 7 families. Genetic mutations are specified in Online Table 1. Twenty-seven patients from 3 families were described previously in brief in the first report on AOS (5). Table 1 presents the baseline characteristics of the study population. Two patients (62 and 64 years of age) had hypertension and used antihypertensive drugs.

Table 1 Baseline Characteristics

Covariates	AOS Patients (n = 44)
Age, yrs	42 ± 17
Male	24 (55)
Height, cm	181 ± 13
Weight, kg	78 ± 15
Body mass index, kg/m^2	24 ± 4
Blood pressure, mm Hg	
Systolic blood pressure	124 ± 14
Diastolic blood pressure	74 ± 8
Mean arterial pressure	92 ± 11
Oxygen saturation, %	98 ± 1
Smoking*	
Never	24 (73)
Current	6 (18)
Former	3 (9)
Creatinine, μmol/l*	72 ± 11

Values are mean ± SD or n (%). *Smoking status and creatinine measurements could be obtained from only 33 patients.
AOS = aneurysms-osteoarthritis syndrome.

Survival. Fifteen deaths in AOS patients with confirmed pathogenic *SMAD3* variants occurred at a mean age of 54 ± 15 years. Autopsy confirmed an aortic dissection as cause of death in 6 patients. In the 9 other patients, no autopsy was performed, but 3 patients were known previously to have aortic aneurysms or dissections. Causes of death with age at time of death are specified in Online Table 1. No intracranial hemorrhage as the cause of death has been reported.

Aneurysms, dissections, and arterial tortuosity in the thorax and abdomen. In 27 (71%) of 38 patients, an aortic root aneurysm was found (range: 36 to 63 mm, *z*-score: 2.9 to 13.2) (Fig. 1A, Online Video 1, Online Figs. 1 and 2). For 6 patients, we did not have aortic dimension data because they died before TTE or CTA could be performed. In 8 (33%) of 24 patients, aneurysms in other arteries in the thorax and abdomen were diagnosed: descending thoracic and abdominal aorta (100 mm), pulmonary trunk (50 mm), superior mesenteric, splenic (40 mm), celiac, hepatic, and common, external and internal iliac arteries (80 mm) (Fig. 1B, detailed information in Online Table 1, Online Figs. 3 and 4). Arterial tortuosity throughout the great vessels of the abdomen and thorax was present in 48% (11 of 23) (Online Video 2).

Mean aortic diameters measured by CTA and TTE are shown in Table 2. The aorta was dilated most often at the level of the sinus of Valsalva. CTA aortic diameter measurements correlated well with TTE (sinus of Valsalva: $r = 0.939$, $p < 0.001$). Two (33%) of 6 evaluated children had aortic diameter *z*-scores that were higher than the normal range according to age ($z + 2.9$ in a 16-year-old boy and $z + 3.3$ in a 15-year-old girl).

Thirteen patients with a mean age of 46 ± 10 years were diagnosed with 1 or more aortic dissections. Stanford type A aortic dissection was diagnosed in 11 patients (Fig. 1A, Online Fig. 2). In 8 patients, this was the first manifestation of the disease. Range of sinus of Valsalva diameter measured before aortic root dissection occurred was 40 to 63 mm (reliable aortic measurements before dissection were available only for 5 patients). Stanford type B aortic dissection was diagnosed in 2 patients (Fig. 1B, Online Video 3, Online Fig. 3). In addition, 2 patients were diagnosed with both a type A and B dissection at different time points.

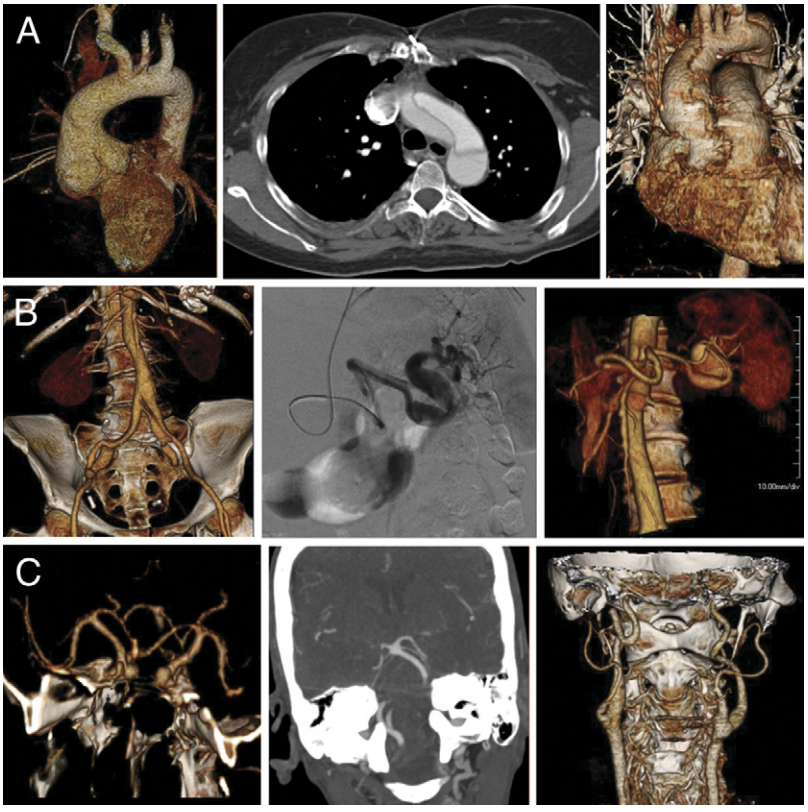

Figure 1 **Cardiovascular Abnormalities throughout the Body in Patients with Aneurysms-Osteoarthritis Syndrome**

(A) Thorax: **(left)** aneurysm of the aortic root (54 mm) in 31-year-old man, and **(middle and right)** Stanford type A aortic dissection at a maximal aortic diameter of 40 mm in a 50-year-old woman. **(B)** Abdomen: **(left)** aortic dissection at a maximal abdominal aortic diameter of 24 mm with dissection flap extending into the left common iliac artery (true lumen in internal iliac artery and false lumen in external iliac artery) and aneurysm in the right common iliac artery (27 mm) and right external iliac artery (16 mm) in 45-year-old woman; **(middle and right)** tortuosity and aneurysm in left splenic artery (21 mm) in the same 45-year-old woman. **(C)** Head and neck: **(left)** 2 saccular aneurysms in the left and right carotid siphon in a 31-year-old man; **(middle)** fusiform aneurysm of the top of the basilar artery in a 26-year-old man; and **(right)** tortuosity of the internal carotid artery in a 34-year-old man. Also see Online Videos 1, 2, 3, and 4.

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Table 2 Outcome Measurements

Covariates	AOS Patients
Electrocardiography (n = 31)	
Heart rate, beats/min	67 ± 12 (50–90)
PR interval, ms	159 ± 24 (136–204)
QRS duration, ms	101 ± 10 (90–118)
Echocardiography (n = 31)	
Left atrial diameter, mm	37 ± 5 (26–49)
Interventricular septal thickness, mm	10 ± 2 (9–15)
Left ventricular posterior wall thickness, mm	10 ± 2 (8–14)
Left ventricular wall mass, g	204 ± 75 (135–342)
Left ventricular end-diastolic diameter, mm	52 ± 8 (40–64)
Left ventricular end-systolic diameter, mm	33 ± 5 (25–42)
Fractional shortening, %	36 ± 7 (28–48)
Peak E velocity, m/s	0.6 ± 0.2 (0.3–0.9)
Peak A velocity, m/s	0.5 ± 0.1 (0.3–0.7)
Transmitral E/A ratio	1.5 ± 0.5 (0.5–2.2)
E-wave deceleration time, ms	233 ± 82 (134–420)
Aortic diameters, mm	
Annulus	26.8 ± 3.1 (20–31)
Sinus of Valsalva	40.1 ± 8.2 (30–50)
Sinotubular junction	31.9 ± 4.8 (27–38)
Proximal ascending aorta	32.8 ± 4.5 (27–46)
Computed tomography angiography (n = 38)	
Aortic diameters, mm	
Annulus	29.8 ± 5.9 (23–38)
Sinus of Valsalva	41.4 ± 8.2 (30–63)
Sinotubular junction	32.0 ± 4.9 (27–38)
Ascending thoracic aorta	32.4 ± 5.2 (28–39)
Aortic arch	25.6 ± 5.4 (19–34)
Descending thoracic aorta	24.9 ± 4.5 (20–32)
Diaphragmatic level aorta	22.2 ± 5.0 (16–28)
Abdominal aorta	22.3 ± 5.3 (15–100)

Values are mean ± SD (absolute range).
E/A = early/late atrial velocity; Other abbreviation as in Table 1.

None of these aortic dissections occurred during the 23 pregnancies and deliveries in our AOS cohort. In 1 patient, a dissection in a nondilated proximal left anterior descending coronary artery was found.

Elective cardiovascular operations and interventions. Fifteen patients underwent 1 or more elective cardiovascular interventions at a mean age of 41 ± 11 years: 12 valve-sparing aortic root replacements, 1 Bentall procedure, 2 splenic artery coiling procedures, and 1 abdominal aneurysm repair; 1 patient underwent aortic repair surgeries in thorax and abdomen and mitral valve repair. In 2 patients, postoperative complications occurred: 1 patient had painful splenic ischemia for which reoperation was necessary and another patient had a total atrioventricular block after valve-sparing aortic root replacement, for which pacemaker implantation was necessary.

Aneurysms and tortuosity of brachiocephalic and intracranial vasculature. CTA of the brachiocephalic and intracranial vasculature was performed in 16 patients with a mean age of 37 ± 14 years. In 56% (9 of 16), we found cerebrovascular abnormalities (detailed information in Online Table 2). Six patients (38%) were diagnosed with 1 or more intracranial aneurysms (Fig. 1C, Online Figs. 5 and 6). Tortuosity of brachiocephalic and intracranial vessels was found in 50% (8 of 16) of the patients (Fig. 1C, Online Video 4, Online Fig. 7). Thirty-one percent of patients (5 of 16) had a combination of aneurysms and tortuosity. In addition, 1 patient showed multiple caliber changes of both intracranial and extracranial vessels. In 7 patients, no cerebrovascular abnormalities were found. Two patients were reported to have had a nonfatal stroke at 56 and 76 years of age, respectively, but it is unclear from their medical histories whether these were ischemic or hemorrhagic strokes.

Cardiac abnormalities. In 18 (51%) of 35 patients, 1 or more mitral valve abnormalities were diagnosed (5 prolapse; 5 billowing; and 5 mild, 2 moderate, and 3 severe cases of mitral valve regurgitation). In 2 patients, structural congenital heart defects were found: 1 patient had an atrial septal defect and persistent ductus arteriosus and another patient had mild congenital pulmonary valve stenosis (peak velocity: 1.82 m/s) and persistent ductus arteriosus. A remarkable finding in this patient was a saccular aneurysm within the persistent ductus arteriosus (7). In addition, 1 patient was found to have a bicuspid aortic valve during surgery.

Left ventricular systolic function and mitral inflow patterns were normal in all patients (Table 2). Left ventricular hypertrophy was present in 19% (6 of 31), with a mean interventricular septal thickness of 12 ± 2 mm, a mean left ventricular posterior wall thickness of 12 ± 2 mm, a mean left ventricular mass of 296 ± 84 g, and mean body surface area-indexed left ventricular mass of 146 ± 34 g/m^2. None of these patients had hypertension, aortic coarctation, or aortic stenosis.

Rhythm disturbances. Electrocardiography revealed sinus rhythm in all patients (Table 2). In 5 patients, premature ventricular contractions (≥3) were found. Seven (22%) of 31 patients had a history of at least 1 episode of documented atrial fibrillation (AF).

Aortic stiffness and biochemical measurements. Online Table 3 shows aortic stiffness and biochemical measurements for healthy controls and AOS patients. The aortic pulse wave velocity (aPWV) tended to be higher in AOS patients compared with controls (9.2 ± 2.2 m/s vs. 7.8 ± 1.8 m/s, $p = 0.076$). Compared with reference values controlled for age and blood pressure, 6 (33%) of 18 patients had an aPWV value of more than 2 SDs (8). Aortic diameter and aPWV were not correlated ($r = -0.278$, $p = 0.357$). N-terminal brain natriuretic peptide (NT-proBNP) was higher in AOS patients than in matched controls (94.1 pg/ml, range: 52.5 to 172.9 pg/ml vs. 12.7 pg/ml, range: 8.5 to 55.1 pg/ml, $p < 0.001$) and correlated with aPWV ($r = 0.731$, $p = 0.005$).

Associated findings of AOS. Osteoarthritis was confirmed by x-rays in 25 (96%) of 26 patients who underwent orthopedic evaluation, whereas 85% exhibited painful joints. Mean age at osteoarthritis diagnosis was 42 years, whereas

the youngest patient was 12 years of age. Spine, hands or wrists, and knees most often were affected (detailed information in Online Table 1). Pes planus was present in 91% of patients and scoliosis was present in 61%. Other associated anomalies included hypertelorism (31%); abnormal palate (54%); abnormal uvula (52%); hernia inguinalis or umbilicalis (43%); and uterus, bladder, or bowel prolapse (41%). More detailed information about these associated findings will be reported separately (9).

Discussion

AOS is a recently described autosomal dominant connective tissue disorder characterized by aneurysms, dissections, and tortuosity throughout the arterial tree in combination with osteoarthritis and mild craniofacial features. The AOS phenotype may resemble that of other connective tissue disorders such as MFS and LDS (Online Table 4). The main site of aortic aneurysms in AOS is the sinus of Valsalva. Similar to LDS, AOS is an aggressive disease with substantial mortality and a high risk of aortic rupture and dissection in mildly dilated aortas (10). AOS and LDS both are associated with widespread arterial tortuosity and aneurysms in the thorax and abdomen (10). In contrast to MFS, cerebrovascular abnormalities frequently occur in AOS and LDS (11). Identification of the underlying genetic defect in TAAD patients is crucial, considering the variability in prognosis, treatment strategy, and risk assessment in family members.

Cardiac abnormalities in AOS. In addition to the aneurysms and tortuosity of the arterial tree, we also found cardiac abnormalities. A remarkable finding in approximately one fifth of the patients was left ventricular hypertrophy in the absence of hypertension or aortic stenosis. Primary cardiomyopathy is reported in one quarter of MFS patients showing mainly a reduced left ventricular ejection fraction, but only in a minority (2.9%) was LV mass increased (12). Mice studies have determined that TGF-β induces proliferation of cardiac fibroblasts and hypertrophic growth of cardiomyocytes (13). Furthermore, TGF-β neutralizing antibodies were able to attenuate LV hypertrophy, and losartan reduced nonmyocyte proliferation, implying possible therapeutic implications in humans as well (14).

Similar to MFS, mitral valve abnormalities were common in AOS patients, and 22% of AOS patients had a history of AF. Mice studies have shown that TGF-β1–induced myocardial fibrosis in the atria plays an important role in predisposing individuals to AF (15). Atrial fibrogenesis in patients with AF occurs in 2 phases: an early increase, but later loss of responsiveness to TGF-β1, while the fibrosis progresses (16).

Furthermore, evidence from mouse studies suggests that TGF-β signaling is essential in the embryogenesis of the heart, valvular pathogenesis, and organization of the aortic wall (17,18). In many mouse models with disrupted TGF-β signaling activities, congenital heart defects are present (17). In the future, *SMAD3* knockdown mice will help to explore the mechanism behind the cardiac abnormalities in AOS.

Aortic stiffness and NT-proBNP in AOS. NT-proBNP in AOS patients was elevated compared with that in controls, although none of the patients had extremely high NT-proBNP levels of more than 250 pg/ml. In vivo and in vitro studies have shown that treatment with brain natriuretic peptide can attenuate cardiac hypertrophy via the TGF-β1 pathway (19). One may hypothesize that the elevated NT-proBNP levels in AOS patients in fact are a protective mechanism against the emergence of LV hypertrophy. Because (mildly to moderately) elevated NT-proBNP levels in other patient groups are reported to predict cardiovascular outcome and AF recurrence, evaluation of the prognostic value of NT-proBNP in AOS patients with respect to clinical outcome may be important (20,21).

The aPWV as a measure of aortic stiffness was high-normal in AOS patients, as was described previously in, for instance, patients with MFS and bicuspid aortic valve (22,23). Ascending aortic diameter and aPWV were not correlated, suggesting that arterial stiffness occurs independently of aneurysm formation. In MFS patients, an augmentation index of more than 11% has been reported to predict progression of aortic diameters, so further research is warranted to test whether this also holds true for AOS patients (24).

Clinical suggestions for cardiologists treating AOS patients. Although AOS is a recently discovered aneurysm syndrome and the full spectrum of the disease and its progression need to be clarified, some preliminary suggestions may be derived from the current findings. Because multisystem involvement frequently is observed, cooperation in a multidisciplinary team with clinical geneticists, cardiologists, orthopedic surgeons, radiologists, neurologists, and, when necessary, (vascular or cardiothoracic) surgeons is important.

MONITORING AND SCREENING. Cardiologists should suspect AOS in every TAAD patient without molecular diagnosis or known cause and should test these patients for *SMAD3* mutations. Furthermore, we suggest that clinicians treating patients with arterial aneurysmal disease in any large artery (intracranial, iliac, splenic artery, and so on) should at least ask whether these patients report joint symptoms. In the physical examination, one must pay special attention to presence of AOS-associated findings, such as joint anomalies and abnormal uvula.

Extensive cardiovascular evaluation using echocardiography and CTA or magnetic resonance imaging (head to pelvis) is recommended in every adult AOS patient. Initially, these diagnostic investigations should be performed annually to determine rate of progression. Thereafter, frequency of imaging should be guided by the findings, for instance, annually if the aortic diameter is more than 35 mm or if the aortic diameter shows significant growth (>5 mm/year).

The phenotype seems to be age-dependent, because aneurysms mainly and dissections only occurred in adult-

hood; however, our series included only 6 children with AOS. Concerning screening in childhood, clear suggestions are difficult to formulate at this time. We suggest that frequency of cardiologic evaluation with TTE, magnetic resonance imaging, or both must be guided by the aortic root *z*-score and presence of other cardiac abnormalities.

Although in our cohort no dissections occurred during pregnancy or delivery, pregnancy should be considered high risk in AOS patients with aneurysms, as in those with MFS and LDS (25).

TREATMENT. The implication of TGF-β signaling in the pathogenesis of aortic aneurysm syndromes suggests a TGF-β antagonist as a specific pharmaceutical target (26). Although losartan showed promising results in MFS mouse models, we have to await the results of randomized clinical trials in MFS, *SMAD3* knockdown mice, and consequently AOS clinical trials (26). At the moment, attention should be focused on genetic counseling, screening of relatives, and interventional or surgical treatment. Medical treatment with losartan, beta-blockade, or both may be beneficial. Stringent control of hypertension to limit aortic wall stress is recommended (27).

Because dissections in AOS patients can occur at relatively small aortic diameters, early elective surgical intervention is indicated to reduce the risk of mortality. Because data are limited and the rate of progression is unknown, we suggest applying the surgical recommendations for LDS (27). Valve-sparing aortic root replacement using the reimplantation technique is the intervention of choice (28). For peripheral aneurysms, individual size or rate of growth and location must determine the treatment strategy.

Currently, the risk of rupture of intracranial aneurysms associated with AOS is unknown. No deaths resulting from intracranial hemorrhage occurred in our series. Life expectancy and size, location, and rate of growth of the aneurysm are the most important determinants to decide whether intervention is needed.

Study limitations. First, the number of subjects included in the present study is relatively small, because AOS has been discovered only recently. Second, the population is quite heterogeneous, particularly in disease severity and age, and because of logistical reasons and mortality, it was not possible to perform every examination in all 44 patients. Further research is necessary to confirm our findings and to gain more insight in the disease mechanism and progression.

Conclusions

AOS is an aggressive, inherited, connective tissue disorder characterized by arterial tortuosity, aneurysms, and osteoarthritis. Aortic root enlargement is the most common cardiovascular finding in our series, but cerebrovascular abnormalities were also present in more than 50% of patients. Aortic dissections occur at smaller diameters than observed in, for instance, MFS, and as such need early elective surgical treatment. Larger prospective follow-up studies are warranted to determine progression over time and clinical relevancy of the cardiac and intracranial abnormalities.

Acknowledgments

The authors thank the participating patients, their families, and their referring physicians. The authors also thank all control subjects and technician assistants from the participating centers.

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Key Words: aneurysm ■ aorta ■ cerebrovascular disorders ■ genetics ■ *SMAD3*.

APPENDIX

For an expanded Methods section and for supplementary figures, videos, and tables, please see the online version of this article.