ISSN 0393-974X/2017

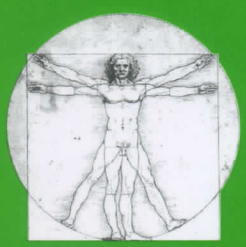
2015
(ISI) IMPACT
FACTOR
1.469

Journal of
BIOLOGICAL REGULATORS
& Homeostatic Agents

JBRHA

Volume 31, No 2, April - June, 2017

Antonio Fontanesi – *L'Arno a Santa Trinità* – 1867 – Galleria d'arte Moderna, Firenze



Published by
Biolife

www.biolifesas.org

JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 31, no. 2, 473-479 (2017)

LETTER TO THE EDITOR

D'ANDREA'S DISEASE (ANGIOMEGALY): A CURRENTLY WELL-DEFINED NOSOLOGICAL ENTITY

S. TAURONE[1], M. SPOLETINI[1], F.M. DI MATTEO[2], R. MELE[2], L. TROMBA[2], F.R. GRIPPAUDO[3], A. MINNI[1] and M. ARTICO[1]

[1]Department of Sensory Organs, [2]Department of Surgical Sciences, [3]Plastic Surgery Department, School of Medicine and Psychology, S. Andrea Hospital, "Sapienza" University of Rome, Rome, Italy

Received October 5, 2016 – Accepted February 14, 2017

The first two authors contributed equally to this article

In 1997 D'Andrea et al. described a new nosological entity the characteristics of which consisted of lengthening, dilation and tortuosity of blood vessels, arteries or veins, less prominent, but also less circumscribed than an aneurysm. This condition does not necessarily imply specific aneurysm formation although aneurysms at multiple sites are a frequent observation. The term used by authors for angiomegaly of the venous system was venomegaly and the analogous condition of the arterial system was termed arteriomegaly. Although tortuosity and dilation of arteries and veins have been widely reported, suggesting a systemic disorder which affects the structural integrity of all vessels, most papers dealing with this intriguing condition did not describe any alterations in the components of vessel walls. In the present paper, the authors describe a well-defined condition, D'Andrea's Disease (or DD, in this article), analyzing its salient morphological and clinical features and clarifying this pathological condition as a distinct and now well-defined nosological entity.

To the Editor,

D'Andrea's Disease (DD or angiomegaly) is a vascular disorder characterized by elongated and distended blood vessels affecting the arterial (arteriomegaly) and/or venous system (venomegaly). The arterial group, drawn from a large arteriographic series, focuses on a comparison between atherosclerotic arteriopathy and arteriomegaly (Figs. 1, 2). The venous group, drawn from a large ultrasound series of vein disorders, is made up of patients with venomegaly. In venomegaly, symptoms are few or absent and this condition appears to be less frequent than arteriomegaly. In ultrastructural terms, DD is characterized by a specific alteration of the elastic component of the vessel wall. In fact, osmiophil amorphous elastic material is found adjacent to the basement membrane of the myocytes located in the vessel wall and, in these areas, a great number of pinocytotic vesicles can be observed, indicating an abundance of newly created elastic material with production of thick elastic fibers (Figs. 3, 4), showing irregular side protrusions and disruption. Such protrusions have a "moth-eaten" appearance and constitute a typical finding of this peculiar pathological condition. The risk factors for DD are similar to those for abdominal aortic aneurysm formation. Although "normal"

Key words: angiomegaly or D'Andrea's disease, arteriomegaly, blood vessel abnormalities, venomegaly

Mailing address:
Dr Samanta Taurone,
Department of Sensory Organs,
"Sapienza"University of Rome,
V.le del Policlinico 155,
00161-Rome, Italy
e-mail: samanta@yahoo.it

0393-974X (2017)

DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

diameter varies with age, gender, and body habitus, the average diameter of the human infrarenal aorta is about 2 cm, with an upper limit of <3 cm considered normal. Generally speaking, in the majority of patients, an infrarenal aorta exceeding the maximum diameter of ≥3 cm is considered to be aneurysmal. Normally, the diameter of the suprarenal aorta tends to be about 0.5 cm larger than that of the infrarenal aorta.

Abdominal aortic aneurysms are abnormal focal dilations of the abdominal aorta. These lesions are relatively common and have a potentially significant morbidity and mortality. The vast majority of patients thus affected are asymptomatic, but they usually come to medical attention owing to a pulsatile abdominal mass on physical examination or, often, as an incidental finding during abdominal imaging studies. The clinical onset is usually marked by abdominal, back or flank pain. There may also be concomitant thromboembolism leading to symptoms of limb ischemia. Aneurysms that produce symptoms have a high risk of rupture, which is frequently associated with high mortality rates. A diagnosis of abdominal aortic aneurysm should be confirmed by an abdominal ultrasound study to verify the presence of dilation of the abdominal aorta. In symptomatic patients, an abdominal CT scan provides information regarding eventual rupture of the aneurysm, its rapid expansion (serial controls) and whether symptoms are related to the aneurysm or are attributable to other abdominal pathologies.

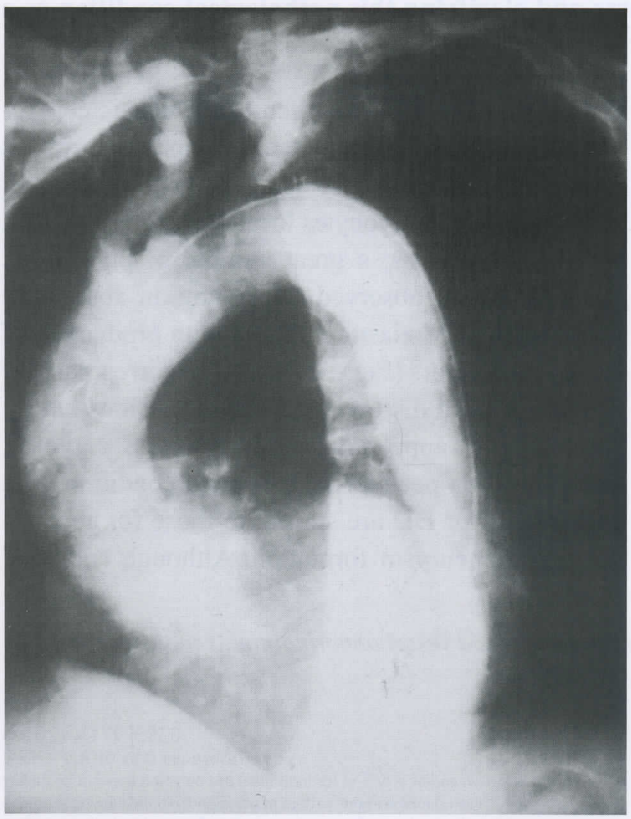


Fig. 1. *Angiogram demonstrating a wide dilation and lengthening of aorta.*

DD is associated with connective tissue disorders, metabolic disorders and fibromuscular dysplasias. Other authors have postulated that a familial association exists for aneurysmal disease. Indeed, some authors have suggested that it might be beneficial to screen family members of patients affected by arteriomegaly and/or peripheral arterial aneurysms.

We reviewed the available literature on this topic and were able to define this nosological entity as a distinct pathological condition (D'Andrea's Disease) with its own particular ultrastructural and histopathological features.

Clinical series

In their study, D'Andrea et al. reported that the abnormality of DD consists of the alteration of the elastic component of the vessel wall (1). Furthermore, Mesh and Graham (2) suggested that both isolated and multiple aneurysms represent different stages or patterns in the process of degenerative deformation resulting from elastin digestion in those segments. In the study described by Cohen et al. (3), the concentration of α1-antitrypsin, a major inhibitor of elastase, was lower in the aneurysmal wall of patients with multiple aneurysms than in those with isolated aneurysms. Therefore, DD may be an expression of a systemic degenerative disease, although the underlying genetic disorder and its aetiology are poorly understood. Yamamoto et al. (4) found no microscopic differences in the aneurysm walls of arteriomegalic vessels compared to non-arteriomegalic ones. It has been suggested that, in addition to atherosclerotic stimuli, other unknown systemic or constitutional factors may be involved in the formation of aneurysms associated with

arteriomegaly, in contrast to those not associated with arteriomegaly. This is supported by the observation that peripheral arteries, which are usually resistant to atherosclerotic disease, such as the brachial and distal external carotid arteries, are dilated in aneurysmal disease in comparison to controls (5). These results support the notion of a generalized dilating diathesis in aortic aneurysmal disease that may have no relationship with atherosclerosis. DD is a progressive disease affecting the arterial tree and is associated with diffuse aneurysmal changes. Doubts still exist regarding the natural history of the disease (6).

MATERIALS AND METHODS

A total of 1,221 consecutive peripheral arteriograms performed on 826 men and 395 women (mean age 68.6 years) to study asymptomatic or symptomatic aneurysms

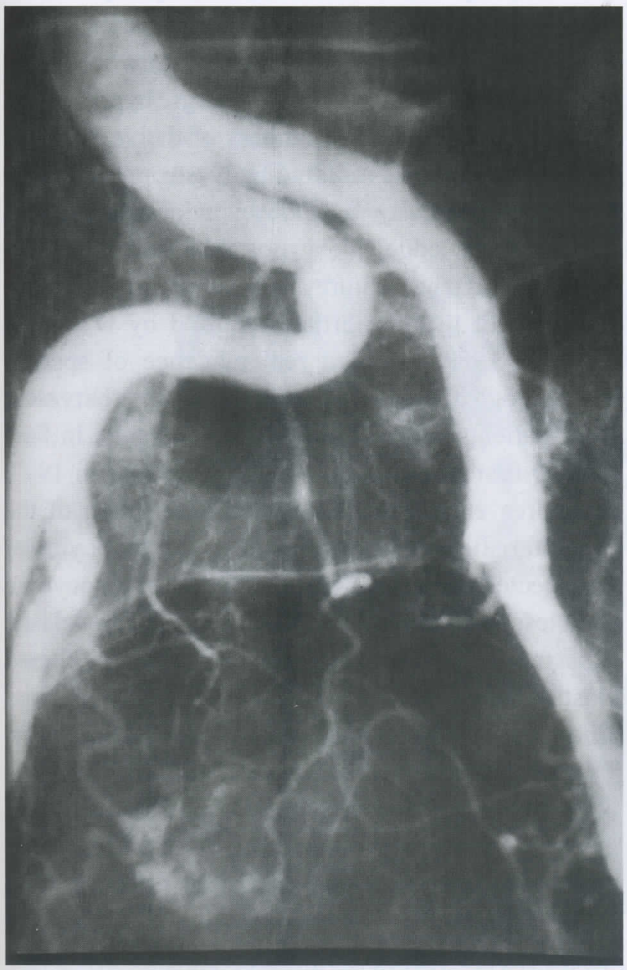


Fig. 2. *Iliac megadolichoarteries: arteriographic picture.*

and thrombo- obliterative disorders of the aorta and its branches were reappraised. Ultrasonographic examination was also performed on 435 patients, and 122 patients underwent CT scan for evaluation of coexisting aneurysms of the abdominal and/or thoracic aorta. The term mega-dolichoartery was used for arteries which appeared diffusely dilated, elongated and tortuous, while arteries which were only diffusely tortuous and elongated, but not dilated were termed dolichoarteries, and those with only diffuse dilatation, but not elongated megarteries. Arteries with duplex and color-elongation but not dilatation were classified as dolichoarteries, and those with only diffuse dilatation but not elongation as megarteries. Using duplex and color-Doppler ultrasound scanners, we were able to study patients whose signs and symptoms of phlebostasis were not attributable to any obvious venous disease, who had no apparent varices and no history of venous thrombosis. We examined a consecutive series of 703 patients, 389 men and 314 women (mean age 55.9 years), by means of an Autosector V duplex scanner with 10 MHz probe and 7-3 MHz multifrequency probe and one group of patients by means of a color-Doppler scanner (Quantum, Acusom).

The ultrasonographic examinations were performed with the patients lying down, sitting and standing: the morphology and valvular function of the great veins of the abdomen, of the lower and upper limbs, and of the neck were studied. Two hundred and eighty-one patients (40%) also underwent venography of the lower limbs. We distinguished five groups based solely on the morphology of the vessels: i) megaveins with valvular continence; ii) megaveins associated with megadolichoarteries; iii) megaveins with valvular laxity; iv) valvular aplasia; and v) valvular laxity.

The last two groups were eliminated because we felt that they did not strictly fall within the classification of venomegaly. A total of 100 relatives of 6 patients with angiomegaly and surgically treated for arteriomegaly were examined by means of a color-Doppler scanner (Quantum, Acusom) to detect the presence of any asymptomatic vascular abnormalities.

In these six patients, during surgery, small tissue blocks were harvested from megadolichoarteries and megaveins for electron microscopic evaluation. Specimens of normal left colic artery and vein were also taken from 3 patients operated on for rectal cancer and from 2 patients operated

on for perforated diverticulum of the sigmoid colon in whom there were no signs of vasculopathy. Fixation was achieved by immerging the small tissue blocks in 2.5% glutaraldehyde in 0.05 M cacodylate buffer (pH 7.2) for 2 hours and postfixing then in 2% osmium tetroxyde in the same cacodylate buffer. The material was then dehydrated with acetone. After embedment in EPON, the material was cut using an LKB ultratome. The semithin sections were stained with toluidine blue and examined by light microscopy. The contrasting of ultrathin sections was performed in the usual way, namely using uranylacetate and lead citrate. No specific contrasting method for elastic tissue was used. Ultrathin sections were examined and photographed using a TESLA BS 500 electron microscope.

Fig. 3. *Transmission electron microscopy: arteriomegaly. Ultrathin section of tunica media of the inferior mesenteric artery. A thick bundle of elastic fibers within the wall of the artery as well as some side protrusions is visible. The fibers, as well as elastic microfibrils, are highly osmiophil (x 21.600).*

DISCUSSION

The first known likely description of angiomegaly dates back to 1571. Julius Caesar Arantius of Vienna (quoted by Michel), was the first to describe a tortuous splenic artery with these words: "*arteriae lienis, ductum obliquum ac flexuosum, anguis in modum*". Although ectatic and elongated arteries in other areas had been finely depicted by anatomists in the 19th century, Leriche (7, 8) in 1942-1943, was really the first to supply a true clinical and arteriographic observation and the first nosographic definition of a clinical pattern that today orients toward a condition, D'Andrea's Disease, previously considered to be a mere anatomical variant. Notwithstanding extensively described case series, such as those reported by Thomas (9) and Hollier et al. (10), no specific morphological alterations of the affected vessels were actually reported in the literature. In this context, the first attempt was the one made in 1919 by Schmidt (11) who, on the strength of light microscopy findings, hypothesized an alteration of the elastic fibers of the vessel wall. Further experiences reported by Nystrom (12), Uitto (13) and especially by Dobrin et al. (14), added further knowledge to a possible morphological definition of the features typical of angiomegaly. However, it was the article reported by D'Andrea et al. (1) that provided real evidence of specific morphological findings in the vessels harvested from patients operated on for angiomegaly. In fact, in their first extensive publication reported in 1997, D'Andrea et al. gave a detailed description of the characteristic alterations found in the myocytes of the affected vessels wall. The presence of pinocytotic vesicles (indicating neoformation of an elastic substance) and the large accumulation of altered elastic fibers and irregular amorphous material among the myocytes penetrating the elastic intima, are the clear and distinctive morphological features of this disease. These findings distinguish the typical electron microscopic appearance of DD. The above-mentioned alterations are markedly different from those observed in atherosclerosis, in which the tunica media contains lipid, cholesterol inclusions and foam cells, absent in the morphological pattern

distinctive of DD. In arteriomegaly the main changes are found in the elastic matrix. Whereas the myocytes do not show any significant damage. In some zones, the collagen microfibrils present an increase in number, but they do not seem to replace degenerated myocytes. In atherosclerosis, on the other hand, the tunica media contains numerous lipid and cholesterol inclusions together with foam cells. A high degree of pinocytotic activity has been observed in the endothelial cells. Myocytes penetrate the elastic intima; their cytoplasm indicates signs of pathological processes (lipid inclusions, vacuoles, increased numbers of mitochondria). In DD, ultrastructural examination using Transmission electron microscopy documented the presence of evident changes in the elastic material of the tunica media and tunica adventitia. Osmiophil amorphous elastic material can also be found in the vicinity of the basement membrane of the myocytes. The latter cells present a great number of pinocytotic vesicles owing to an abundant production of newly altered elastic material. Thick elastic fibers showing irregular side protrusions have also been observed: moreover, highly osmiophilic elastic material has been observed between the myocytes of the media and the adventitia. These findings are substantially analogous both in arteriomegalic and venomegalic patients; in subjects with venomegaly, however, the above-mentioned alterations can be found in all layers of the examined venous wall. This last observation seems to suggest that the alteration is more marked in the wall of veins (probably due to their different structure in comparison to arteries). The latter finding could explain the more pronounced dilation and tortuosity of the venous lesions in DD revealed by spiral CT and magnetic resonance imaging (MRI). The role of anatomical and mechanical factors is extremely important in this degenerative process. Inflammation may disrupt the balance in the protease/antiprotease system, contributing to the degenerative process. The possibility that DD is not only a local vascular disease, but also a generalized process in the vascular system has recently been emphasized by authors who documented defects in the mechanical properties of the vascular wall of distant arteries not prone to dilatation (15-17). Furthermore, the regulation of blood flow (i.e., the arteriolar resistance function) also seems to be disrupted (18). In earlier studies, a tendency towards a general dilatation of the peripheral arteries in patients with DD was

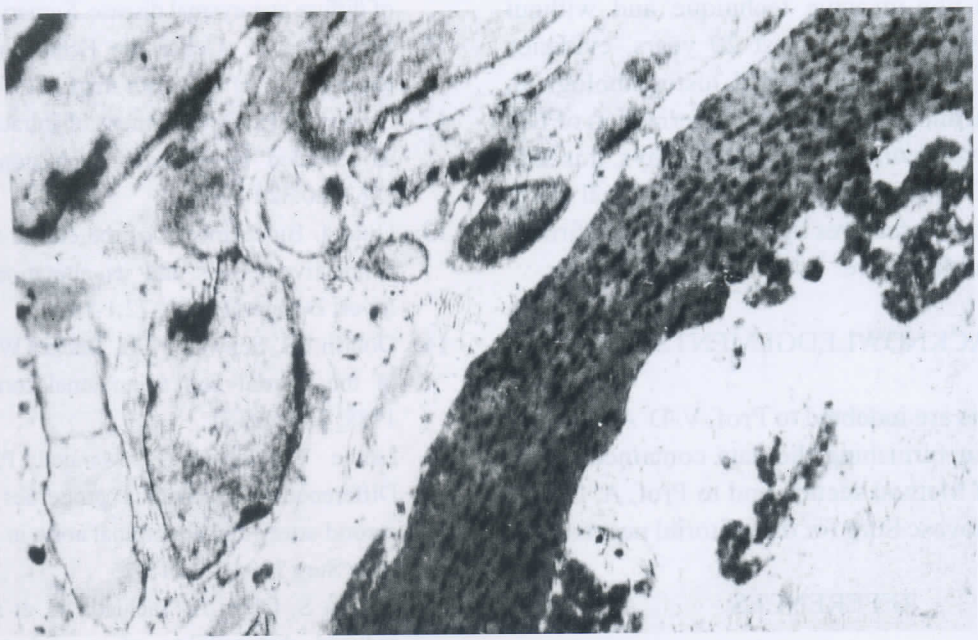


Fig. 4. *Transmission electron microscopy: arteriomegaly. Ultrathin section of tunica media of the inferior mesenteric artery showing highly osmiophil elastic fibers with some disruptions of their integrity (x 40.000).*

reported. Recently, it was shown that the diameters of peripheral arteries increase by about 20% to 25% in patients aged between 20 and 70 years (19).

Generally speaking, the size of an artery depends on both sex and body habitus. Anatomical and mechanical factors are important in this degenerative process, and the onset of an inflammatory process may disrupt the balance of the protease/anti-protease system. In peripheral parts of the vasculature, such as the subcutaneous arterioles, there are alterations in the blood-flow regulation that might be attributed to a defective function of the elastin-containing arteriolar walls (18). The diameter of major vessels increases during lifetime, not only during the period of body growth, but also as a result of degeneration and remodeling of the arterial wall in adults (20-21). In fact, the arterial diameter is dependent on age and body size, as emphasized by Barandiaran et al. in a recent interesting study on angiomegaly (22).

Duplex and color-Doppler scanning may be useful tools for systematic monitoring of patients with DD, but a relevant contribution to diagnostic assessment of this disease is made by CT (especially spiral CT) and, above-all, by MRI. Typical DD vessel alterations (i.e. lengthening, dilation and tortuosity of blood vessels) may be clearly detected by MRI, employing a non-invasive technique and without significant risks. Over the last 20 years, evidence of a distinct and clearly defined histopathological, ultrastructural and diagnostic characterization of DD has progressively come to light. Nowadays, it is safe to say that DD is a distinct clinico-pathological entity with characteristic features that have been confirmed by the relevant literature.

ACKNOWLEDGEMENTS

The authors are indebted to Prof. V. D'Andrea for his courtesy in furnishing the data contained in the Materials and Method section and to Prof. A. Oliaro and to J Cardiovasc Surg for the editorial permission.

REFERENCES

1. D'Andrea V, Malinovsky L, Cavallotti C , et al. Angiomegaly. J Cardiovasc Surg 1997; 38(5):447-55.
2. Mesh CL, Graham LM. Aortic Aneurysms, Arteriomegaly and Aneurysmosis In: Ernst CB, Stanley JC ed. Current Therapy in Vascular Surgery 3rd ed. St Louis; Mosby 1995; p 292-96.
3. Cohen JR1, Mandell C, Chang JB, Wise L. Elastin metabolism of the infrarenal aorta. J Vasc Surg 1988; 7(2):210-14.
4. Yamamoto N, Unno N, Mitsuoka H, Ukiyama T, Saito T, Kaneko H, Nakamura S. Clinical relationship between femoral artery aneurysms and Arteriomegaly. Surg Today 2002; 32:70-73.
5. Ward AS. Aortic aneurismal disease. A generalized dilating diathesis. Arch Surg1992; 127:990-91.
6. Barandiaran JV, Hall TC, Glaves I, El-Barghouti N, Perry EP. An observational study into the management of arteriomegaly: a call for a revised classification system. Ann R Coll Surg Engl 2012; 94(4):250-55.
7. Leriche R. Dolicho et méga-artére: dolicho et mégaveine. Prèsse Med 1943; 51:554-5.
8. Leriche R. Dilatation pathologique des artères endehors des anéurysmes vie tissulaire des artères. Prèsse Med 1942; 50:641-42.
9. Thomas ML. Arteriomegaly. Br J Surg 1971; 58:690-93.
10. Hollier LH, Stanson AW, Gloviczki P, et al. Arteriomegaly: classification and morbid implications of diffuse aneurysmal disease. Surgery 1983; 93:700-8.
11. Schmidt MB. Ueber die Schlagelung der Arteria temporalis. Zbl Allg Path Anat 1919; 30:49-56.
12. Nystrom SH. Development of intracranial aneurysm as revealed by electron microscopy. J Neurosurg 1963; 20:329-37.
13. Uitto J. Biochemistry of the elastic fibers in normal connective tissues and its alteration in diseases. J Invest Dermatol 1979; 72:1-10.
14. Dobrin PB, Schwarcz TH, Backer WH. Mechanisms of the arterial and aneurysmal tortuosity. Surgery 1988; 104:568-71.
15. Länne T, Hansen F, Mangell P, Sonesson B. Differences in mechanical properties of the common carotid artery and abdominal aorta in healthy males. J Vasc Surg 1994; 20:218-25
16. Makita S, Ohira A, Tachieda R, et al. Dilation and reduced distensibility of carotidartery in patients with abdominal aortic aneurysms. Am Heart J 2000; 140:297-302.

17. Laureys M, Akkari K, De Wilde JP. Arteriomegaly. Cardiovasc Intervent Radiol 2005; 28(3):358-9.
18. Midttun M, Sejrsen, Paaske WP. Is non-specific aneurismal disease of the infra-renal aorta also a peripheral microvascular disease? Eur J Vasc Endovasc Surg 2000;19:625-29.
19. Sandgren T, Sonesson B, Ryden-Ahlgren Å, Länne T. The diameter of the common femoral artery in healthy humans: influence of sex, age, and body size. J Vasc Surg 1999; 29:503-10
20. Glagov S, Vito R, Giddens D, Zarins C. Micro-architecture and composition of artery walls: relationship to location, diameter and the distribution of mechanical stress. J Hypertens 1992; 10 (Suppl 6):S101-4.
21. Baxter T, Davis V, Minion D, Wang YP, Lynch T, McManus B. Abdominal aortic aneurysms are associated with altered matrix proteins of the non aneurismal aortic segments. J Vasc Surg 1994; 19:797-803.
22. Barandiaran JV, Hall TC, Glaves I, El-Barghouti N, Perry EP. An observational study into the management of arteriomegaly: a call for a revised classification system. Ann R Coll Surg Engl 2012; 94(4): 250-55.