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REVIEW

Diagnosis and Management of Genetic Causes of Middle Aortic Syndrome in Children: A Comprehensive Literature Review

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Abstract: Middle aortic syndrome (MAS) is a rare vascular disease representing an important cause of severe hypertension in children. MAS is characterized by segmental or diffuse narrowing of the abdominal and/or distal descending aorta with involvement of the renal and visceral branches. Most cases of MAS are idiopathic, but MAS may occur in genetic and acquired disorders. The most common genetic causes of MAS are neurofibromatosis type I, Williams syndrome, Alagille syndrome, tuberous sclerosis and mucopolysaccharidosis. This review article discusses the pathophysiological aspects, distinctive associated features, and management of genetic forms of MAS in children.

Keywords: middle aortic syndrome, hypertension, neurofibromatosis type 1, Williams syndrome, Alagille syndrome, tuberous sclerosis, mucopolysaccharidoses

Introduction

Definition

Middle aortic syndrome (MAS) is a rare disease characterized by segmental or diffuse narrowing of the abdominal and/or distal descending aorta with involvement of the renal and visceral branches and represents an important cause of severe hypertension in children.[1,2] Ostial stenosis of the major branches of the proximal abdominal aorta is a characteristic in MAS.[3] MAS was described for the first time in 1963 by Sen et al in 16 patients with inflammatory narrowing of the middle aortic segment.[4] It represents 0.5–2% of all cases of aortic narrowing.[3,5]

Etiology

Most cases of MAS are idiopathic, but MAS may occur in genetic and acquired disorders (Table 1).

Genetic Causes of MAS

Genetic forms of MAS are usually described in children and young adults and encountered in 7–36% of the cases.[1,6,7] The most common genetic causes of MAS are neurofibromatosis type I, Williams syndrome, Alagille syndrome, tuberous sclerosis and mucopolysaccharidosis.[8–15] A recent study has been demonstrated that monogenic cause of MAS was present in 43% of 35 families with MAS and whole-exome sequencing revealed mutations in genes previously associated with vascular disease (*NF1, JAG1, ELN, GATA6, RNF213*).[16] The prevalence of genetic diseases associated with MAS in different studies is presented in Table 2.

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Table 1 Causes of Middle Aortic Syndrome in Children

Genetic		Neurofibromatosis type 1
		Williams syndrome
		Alagille syndrome
		Tuberous sclerosis
		Mucopolysaccharidoses
Acquired	Inflammatory	Takayasu arteritis
		Congenital rubella
	Non-inflammatory	Post-surgical fibrosis
		Radiotherapy
Idiopathic		

Table 2 Prevalence of Genetic Forms of MAS in Children

Study	Patients (N)	Genetic Diseases (N/%)	NF1 (N/%)	WS (N/%)	ALGS (N/%)
Panayiotopoulos et al 1996[17]	13	7 (53.8)	4 (30.7)	3 (23.1)	0
Sethna et al 2008[18]	247	17 (6.9)	12 (5)	5 (2)	0
Tummolo et al 2009[7]	36	10 (27.8)	7 (19.4)	3 (8.3)	0
Porras et al 2013[3]	53	21 (39.6)	5 (9.4)	12 (22.6)	4 (7.5)
Ruman et al 2015[1]	630	97 (15.4)	49 (7.8)	41 (6.5)	7 (1.1)
Warejko et al 2018[16]	36	13 (36.1)	6 (16.7)	3 (8.3)	4 (11.1)
Patel et al 2020[19]	13	3 (23)	2 (15.4)	1 (7.7)	0
Total	1028	168 (16.3)	85 (8.3)	68 (6.6)	15 (1.4)

Note: Data from references 1,3,7, and 16–19.
Abbreviations: NF1, neurofibromatosis type 1; WS, Williams syndrome; ALGS, Alagille syndrome.

Acquired Causes of MAS

Acquired inflammatory diseases which can lead to MAS are Takayasu arteritis and other non-specific arteritis and congenital rubella.[3,20–23] Other acquired causes of MAS include post-surgical fibrosis and damage of the vasa-vasorum after surgical resection of an abdominal tumor or impaired growth of the aorta after radiation therapy for neuroblastoma in children.[24,25] Takayasu arteritis is a chronic inflammatory disease with unknown precise etiology, with genetic factors' involvement such as HLA genes and other proposed risk factors as genetic variants in genes encoding immune response regulators and pro-inflammatory cytokines. This form of MAS encountered in 15–18% of the cases.[1,26]

Idiopathic MAS

Most cases of MAS are idiopathic. Congenital cases have been described due to a developmental anomaly in the fusion and maturation of the embryonic dorsal aortas.[5,12]

Vessel Involvement

Commonly, idiopathic MAS involves renal and splanchnic branches of the aorta, and the most common anatomic site of the aorta narrowing is infrarenal.[1,3] MAS determined by genetic disorders is more often associated with suprarenal stenosis and extra-aortic involvement. Renal arteries are involved in 84% of the cases and in 60% of the cases the

stenosis is bilateral, superior mesenteric artery are involved in 44% of the cases, coeliac trunk in 39% of the cases and common iliac artery in 15% of the cases.[1,27]

The incidence and prevalence of MAS estimation is challenging because of the heterogeneity of aortic branches involvement and etiology.

Presentation

Patients with MAS are usually diagnosed during childhood or adolescence. Presentation in infancy has also been reported and has a poor prognosis, especially in preterm infants.[28]

Clinical manifestations are severe hypertension, headache, postprandial abdominal migraine, claudication of the inferior limbs, absent femoral pulses, blood pressure discrepancy between upper and lower extremities, abdominal bruit, and failure to thrive.[7,12,29] Despite the guidelines which strongly recommend regular measurement of the blood pressure in children, arterial hypertension may be an incidentally finding at a routine clinical examination.[30,31]

According to associated disease, these patients can have additional physical examination findings as dysmorphic features, skin spots, jaundice, skeletal abnormalities, and organomegaly. The most common complication of MAS is renovascular hypertension, which can lead to heart failure, left ventricle hypertrophy, dilated cardiomyopathy in infants and neonates, cerebrovascular accidents, renal failure, hypertensive retinopathy, and encephalopathy.[3,32]

Diagnosis

Diagnosis of MAS has increased in the last decades due to improved diagnostic imaging technologies such as angiography, CT angiography, magnetic resonance angiography and ultrasound.[1,3,20,33]

Treatment

Management of MAS includes medical therapy, endovascular and surgical intervention. The most common anti-hypertensive agents are calcium-channel blockers, beta-blockers, diuretics, angiotensin-converting enzyme inhibitors and alpha-blockers, and they are effective in mild or moderate aortic or renal stenosis.[1,3] Medical treatment is very often insufficient. Endovascular interventions such as balloon angioplasty or stenting represent a palliative procedure because of the increased rate of restenosis, but they are performed to avoid surgical intervention on the developing aorta in children. Repeated balloon dilations with paclitaxel eluting balloons have demonstrated to be an effective and safe therapeutic option in a 15-year-old patient.[34] Younger age at the time of intervention could be a risk factor for vascular complication because patients who are diagnosed in the first years of life has a severe form of disease.[3] Surgical procedures are indicated when endovascular interventions fail to achieve the long-term blood pressure values control or when the lesions are too complex for percutaneous transluminal angioplasty. The surgical interventions used for MAS are aorto-aortic bypass grafting, graft vascular replacement, patch angioplasty.[12,35,36] Prosthetic grafts may necessitate replacement in children who are still growing and can determine mechanical complications as thrombosis and aneurysm formation.[12,37,38] A novel technique is represented by tissue expander (TE)-stimulated lengthening of arteries (TESLA), which determines a slow development of the normal distal aorta and the stenotic segment of the aorta can be resected and anastomosis can be performed without a prosthetic graft.[39] In this procedure based on stretch-induced growth a tissue-expanding device is placed behind the child's aorta and it is gradually filled with saline solution for a period of months. During the growth period, the development of the aorta is closely monitored by imaging tests. Another novel technique is represented by Mesenteric Artery Growth Improves Circulation (MAGIC) and consists of an aorta bypass using the mesenteric arteries as a free conduit.[40] Both the MAGIC and TESLA procedures provide feasible approaches for aortic bypass and reconstruction using autologous tissues.

Renovascular hypertension may benefit of renal artery reimplantation, arterial reconstruction with autologous or synthetic grafts, nephrectomy, and auto-renal transplantation.[41,42] Most studies referring to MAS in children include all causes (acquired, genetic and idiopathic) without a detailed presentation of the genetic ones and those referring to genetic forms of middle aortic syndrome in children are scarce and most of them are case reports. Herein, the most encountered genetic diseases associated with middle aortic syndrome are reviewed. Attention is focused on the genetic and

pathophysiological aspects of each disorder with individual description and presentation of distinctive associated features and therapeutic options.

Methods

Search Strategy

A systematic literature search was performed using electronic literature databases (PubMed/Medline and Google Scholar database) and followed Preferred Reporting Items for Systematic Review and Meta-analysis protocol (PRISMA).[43] We excluded conference abstracts and limited the search to literature published in English. We also screened all the reference lists of systematic reviews and meta-analysis to find other relevant eligible publications. We excluded all studies in adults and studies referred to idiopathic or acquired MAS.

Study Selection and Data Extraction

Two independent researchers performed the literature search till June 2021. We selected the concept of "middle aortic syndrome", "mid-aortic syndrome", "genetic", "coarctation of the aorta", "renal artery stenosis", "coeliac trunk stenosis", "mesenteric artery stenosis", "neurofibromatosis", "Williams syndrome", "Alagille syndrome", "tuberous sclerosis", "mucopolysaccharidoses" and "children aged 0–18 years". Search term combinations were used.

The criteria to include the patients and studies in the present systematic review were as follows: 1) age under 18 years; 2) studies that reported patients with MAS and genetic diseases; 3) case reports, case series and observational studies; 4) articles in English; and 5) no restriction regarding the year of publication. The exclusion criteria were as follows: studies that did not present complete data about diagnosis and treatment, reviews, conference abstracts, experimental research. After reading the studies in full, the following data were collected: author, year of publication, study design, the country where the study was conducted, number of patients. Data extraction was targeted to patients' age, clinical findings, vessels involvement, investigations, treatment and outcomes.

Results

The search strategy has identified a total of 475 articles on which only 136 articles met the inclusion criteria. A total of 37 articles of 85 cases, most of them case reports and case series were included in this work. The study selection flowchart is shown in Figure 1.

The patients age ranged 1–17 years. Five genetic diseases associated with MAS were described in this work: 26 patients with neurofibromatosis, 32 patients with Williams syndrome, 15 patients with Alagille syndrome, 4 patients with tuberous sclerosis and 8 patients with mucopolysaccharidoses. Clinical characteristics, vessel involvement and therapeutic options for patients with MAS and neurofibromatosis, Williams syndrome and Alagille syndrome are depicted in Tables 3–5.

Discussion

Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder caused by mutations in the tumor suppressor gene *NF1* which encodes the neurofibromin, which regulates the cell growth and division. Whole-exome sequencing studies revealed that protein truncating mutations (splice site and frameshift mutations) in NF1 may result in MAS.[16]

Loss of neurofibromin produces increased mitogenic signaling and leads to increased cellular proliferation or differentiation. Diagnosis criteria for NF1 are as follows: six or more *café au lait* macules (>0.5 cm at largest diameter in a pre-pubertal child or >1.5 cm in post-pubertal individuals), axillary or groin freckling, two or more neurofibromas or one or more plexiform neurofibromas, two or more Lisch nodules, bony dysplasia, optic pathway glioma and a first-degree relative with neurofibromatosis type 1. Two or more features are required for diagnosis.[68]

Arterial hypertension is a common finding in neurofibromatosis type 1 and is mainly secondary to vascular disease in children and to pheochromocytoma in older ages. Because many patients are asymptomatic, regular blood pressure assessment and ambulatory blood pressure monitoring enables early diagnosis of hypertension and arterial stenosis.

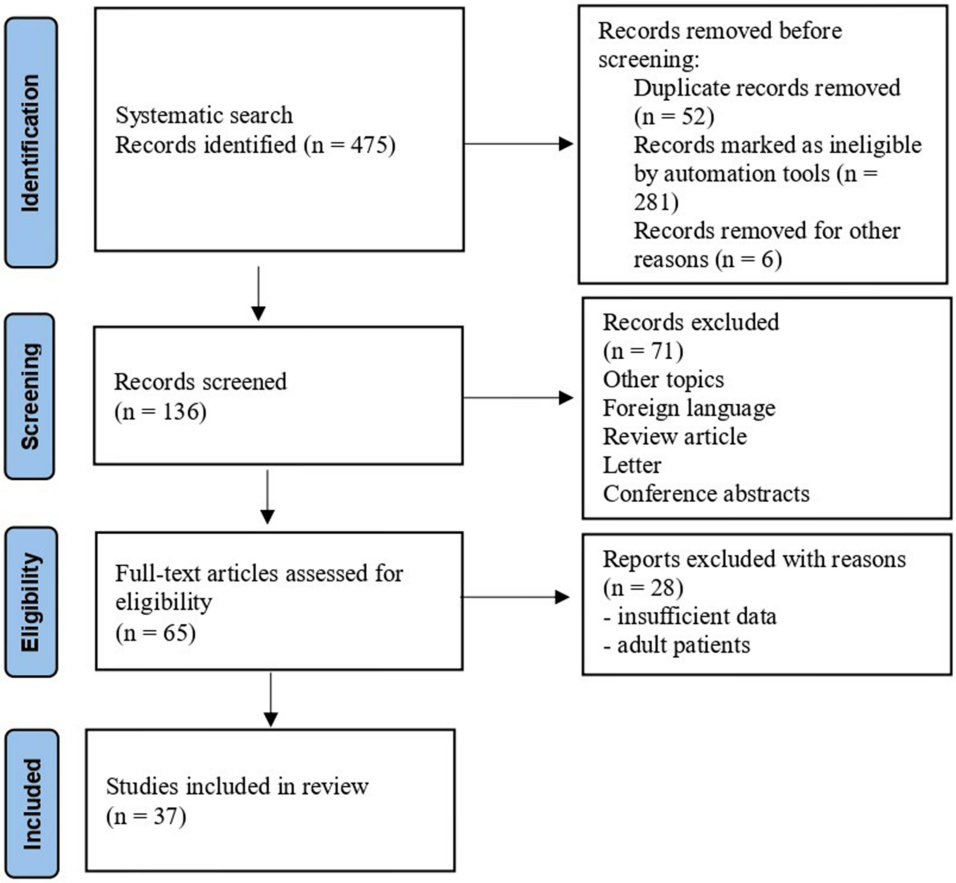

Figure 1 PRISMA flow diagram of study selection.
Notes: Adapted from Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100. doi: 10.1371/journal.pmed.1000100.[43] Copyright: © 2009 Liberati et al. Creative Commons Attribution License.

NF1 is the most common genetic disorder associated with MAS and encountered for 5–22% of the cases.[1,3,6,7,16,17,19] Another study found NF1 as the second cause of MAS after Williams syndrome.[3]

Vascular disease in NF type 1 is determined by loss of neurofibromin expression in the smooth muscle cells and in the vascular endothelium and consists in abnormal proliferative response to arterial injury of the smooth muscle cells and increased neointima formation.[69] Vascular abnormalities include aneurysm, stenosis and arteriovenous malformations and affects 18% of the cases.[44] Pathologic findings in patients with vascular disease revealed fibromuscular dysplasia with neointimal thickening.[45] The true prevalence of vasculopathy in NF-1 is underestimated because most patients are asymptomatic despite multi-vessel involvement and imaging studies are usually reserved for symptomatic patients.

CT angiography and magnetic resonance angiography can diagnose MAS, can determine the location and extent of stenosis of the aorta and its associated visceral branches, as well as the presence of collateral circulation and are also used for postoperative or endovascular intervention follow-up.[70] They can also exclude external compression of the aorta by neurofibromas. The typical string-of-pearls involvement of the renal arteries in fibromuscular dysplasia is not present in neurofibromatosis where the vascular involvement is proximal.[46,47] A routine abdominal ultrasonography with visualization of the abdominal aorta in a longitudinal view, performed by experienced specialist, could be a useful method of diagnosis in children.[48]

The most common arteries involved in NF1 children with MAS are renal arteries (97.1% of cases), superior mesenteric artery (50% of cases) and celiac artery (37.5% of cases) – Table 2.

Figure 2 shows thoracic and abdominal magnetic resonance angiogram revealing reduced caliber of the abdominal aorta and narrowed left renal artery at emergence in a 4-year-old boy with NF1.

Table 3 Characteristics of 26 Children with NF1 and MAS

Parameter			Patients (N/%)	Percent of Missing Data
Age (years)			8.8	35.7
Presentation	Hypertension		17 (100)	39.3
	Headache		5 (29.4)	53.6
	Abdominal pain		4 (23.5)	53.6
	Week femoral pulses		3 (17.6)	53.6
	Claudication		3 (17.6)	53.6
	Asymptomatic		6 (35.3)	39.3
End-organ findings	Cardiac		2 (11.8)	39.3
	Renal		3 (17.6)	39.3
Aortic involvement	Thoracic aorta		0	0
	Abdominal aorta		28 (100)	0
Visceral arteries	Renal artery	Unilateral	10 (40)	0
		Bilateral	16 (57.1)	0
	Superior mesenteric artery		14 (50)	0
	Coeliac		10 (35.7)	0
	Common iliac		0	0
Management	Isolated antihypertensive medication		4 (14.3)	0
	Endovascular	PTA	9 (32.1)	0
		PTA with stent	2 (7.2)	0
	Surgical	Aorto-aortic bypass	11 (39.3)	0
		Reconstruction patch graft	3 (10.7)	0
		Renal auto transplant	3 (10.7)	0
Outcome	Deterioration		7 (26.9)	0
	Improvement		15 (57.7)	0
	NA		4 (15.4)	0

Note: Data from references 5,7,16,17,19, and 44–55.
Abbreviations: NA, not available; PTA, percutaneous transluminal angioplasty.

Treatment of vascular lesions in patients with NF1 includes medical therapy, endovascular and surgical intervention. Very often, hypertension is difficult to control despite multiple antihypertensive agents and may lead to end-organ damage.

The results of balloon angioplasty in children with MAS and NF1 are debated. Srinivasan et al reported similar results to those of children without NF1, with improvement in 84–91% of the cases.[71] In other studies, hypertension was more difficult to treat, and the results were disappointing with cured rate in 33% of the patients.[9] Other studies found that NF1 represents a risk factor for vascular complications from catheter-based interventions such aneurysm and vascular tears because of

Table 4 Characteristics of 32 Children with WS and MAS

Parameter			Patients, N (%)	Percent of Missing Data
Age (years)			10.7	9.4
Presentation	Hypertension		24 (92.3)	18.8
	Headache		2 (7.7)	18.8
	Abdominal pain		1 (3.8)	18.8
	Week femoral pulses		2 (7.7)	18.8
	Claudication		2 (7.7)	18.8
	Asymptomatic		2 (7.7)	18.8
End-organ findings	Cardiac		0	100
	Renal		0	100
Aortic involvement	Thoracic aorta		6	0
	Abdominal aorta		32 (100)	0
Visceral arteries	Renal artery	Unilateral	11 (34.4)	0
		Bilateral	17 (53.1)	0
	Superior mesenteric artery		14 (43.8)	0
	Coeliac		12 (37.5)	0
	Common iliac		1 (3.1)	0
Management	Isolated antihypertensive medication		5 (50)	68.8
	Endovascular	PTA	4 (40)	68.8
		PTA with stent	0	68.8
	Surgical	Aorto-aortic bypass	1 (10)	68.8
		Reconstruction patch graft	0	68.8
		Renal auto transplant	2 (20)	68.8
Outcome	Deterioration		3 (30)	68.8
	Improvement		4 (40)	68.8
	NA		3 (30)	68.8

Note: Data from references 8,16,19,27, and 56–59.
Abbreviations: NA, not available; PTA, percutaneous transluminal angioplasty.

predisposition to develop spontaneous aneurysm. In NF1 structure abnormalities of the arterial walls are common, and these abnormalities will lead to increased risk for vascular complication after vascular intervention.[3,45,72–74] Further dilatation with repeated angioplasty at a later date could lead to recoil, and a weakened arterial wall may result in later aneurysm formation in 5% to 20% of the cases.[74]

Table 5 Characteristics of 15 Children with ALGS and MAS

Parameter			Patients, N, %)	Percent of Missing Data
Age (years)			10	33.3
Presentation	Hypertension		11 (73.3)	26.7
	Headache		0	26.7
	Abdominal pain		0	26.7
	Week femoral pulses		1 (6.7)	26.7
	Claudication		0	26.7
	Asymptomatic		0	26.7
End-organ findings	Cardiac		0	53.3
	Renal		3 (20)	53.3
Aortic involvement	Thoracic aorta		0	0
	Abdominal aorta		15 (100)	0
Visceral arteries	Renal artery	Unilateral	2 (13.3)	0
		Bilateral	6 (40)	0
	Superior mesenteric artery		12 (80)	0
	Coeliac		12 (80)	0
	Inferior mesenteric artery		1 (6.7)	0
	Common iliac		0	0
Management	Isolated antihypertensive medication		6 (40)	53.3
	Endovascular	PTA	2 (13.3)	53.3
		PTA with stent	2 (13.3)	53.3
	Surgical	Aorto-aortic bypass	1 (6.7)	53.3
		Reconstruction patch graft	1 (6.7)	53.3
		TESLA	1 (6.7)	53.3
		Renal auto transplant	1 (6.7)	53.3
Outcome	Deterioration		2 (13.3)	46.7
	Improvement		2 (13.3)	46.7
	NA		4 (26.7)	46.7

Note: Data from references 10,16, and 60–67.
Abbreviations: NA, not available; PTA, percutaneous transluminal angioplasty; TESLA, tissue expander (TE)-stimulated lengthening of arteries.

Williams Syndrome

Williams syndrome (WS) is a rare genetic multisystemic disorder characterized by a distinct facial appearance, cardiovascular anomalies (most frequently supravalvular aortic stenosis, peripheral pulmonary stenosis, stenosis of medium and large arteries, hypertension), cognitive and developmental delay, growth abnormalities, endocrine abnormalities

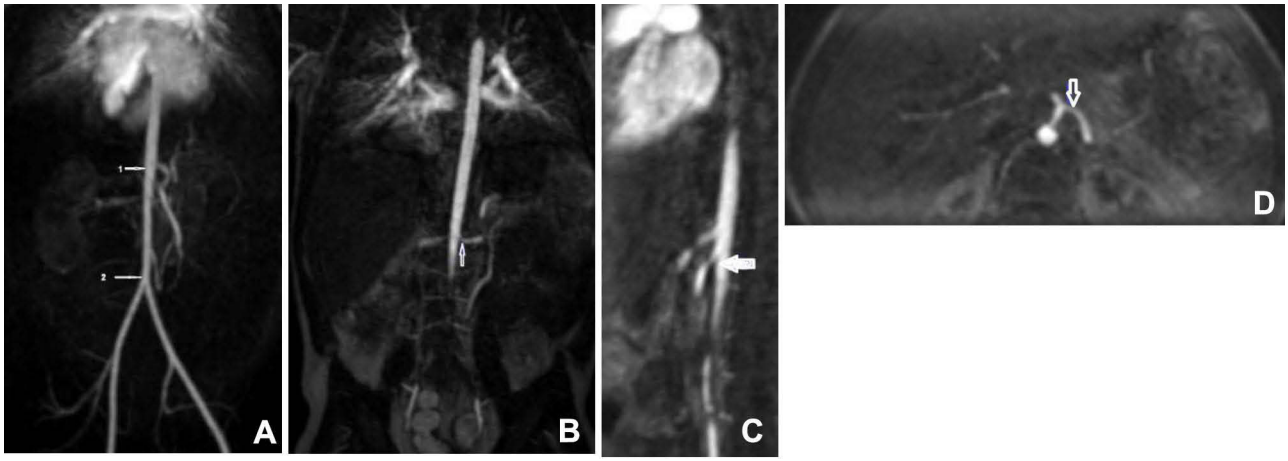

Figure 2 Thoracic and abdominal magnetic resonance angiogram in a 4-year-old boy with NF1 revealing the reduced caliber of the abdominal aorta (**A**), narrowed left renal artery (**B**), superior mesenteric artery (**C**) and celiac trunk at emergence (**D**). The diameter of aorta is 6.9 mm (*Z* score = −2.32) at celiac trunk emergence (arrow 1) and 3.8mm (*Z* score = −6.7) at bifurcation (arrow 2).

(hypercalcemia, hypercalciuria, hypothyroidism and early puberty) and connective tissue abnormalities.[75–77] Williams syndrome is caused by a microdeletion on chromosome 7q11.23, a region containing 26–28 genes including *ELN* gene encoding the elastin.[78]

Hemizygosity of the *ELN* gene has been demonstrated to be responsible for the vascular pathology in WS because of reduced elasticity of the arterial tree and increased arterial stiffness and these mutations were found in individuals with MAS and without other Williams syndrome phenotypic features.[16,79,80] The role of elastin in modulation, proliferation and migration of vascular smooth cells is impaired in WS, and the result of its impaired function is represented by the occlusion of the vascular lumen.[81]

Vascular abnormalities are present in more than 80% of the patients with WS and involve thoracic and abdominal aorta, renal arteries, mesenteric arteries, coronary arteries and intracranial vessels.[79,82,83]

Rose et al found a specific morphology of the aorta in patients with WS and MAS with suprarenal narrowing, stenosis of the renal arteries and increased diameter of the infrarenal lumen. The smallest diameter of the aorta is close to the origin of the renal artery, consisted in renal artery stenosis.[27]

Figure 3 shows thoracic and abdominal CT angiogram revealing reduced calibre of the abdominal aorta and narrowed renal arteries in a 3-month-old infant with WS.

The frequency of MAS in WS is variable in different studies, ranging 2% to 70%.[8,27,56] There is evidence that moderate and severe vascular lesions may have rapid progression over short periods of time.[8,57,74,83,84] Arterial hypertension was found in 22–50% of the patients with WS.[27,82,83]

CT angiography and magnetic resonance angiography are used to diagnose MAS in children with WS and periodic imaging techniques are required in patients with moderate and severe vascular abnormalities characterized by progressive evolution.[85,86] Although hypertension in WS patients has been classically attributed to the renal vascular disease, stenosis of other different vessels must be always considered.

Therapeutic options for vascular lesions in patients with WS include medical therapy, endovascular and surgical intervention. The treatment of systemic hypertension in MAS patients with WS includes calcium channel blockers, beta-blockers and angiotensin-converting enzyme inhibitors, and medical therapy is indicated in small children or in patients with unacceptable level of operative risk. There are little data about the interventional treatment and the timing of surgical intervention is controversial in children. Combined antihypertensive treatment alone was used in half of children with MAS and WS. Interventional treatment was used in the other half of the patients and in 20% of the patients vascular angioplasty was associated with renal auto-transplant. Medical treatment, as has been demonstrated in other studies, has better results than interventional procedures.[1,56]

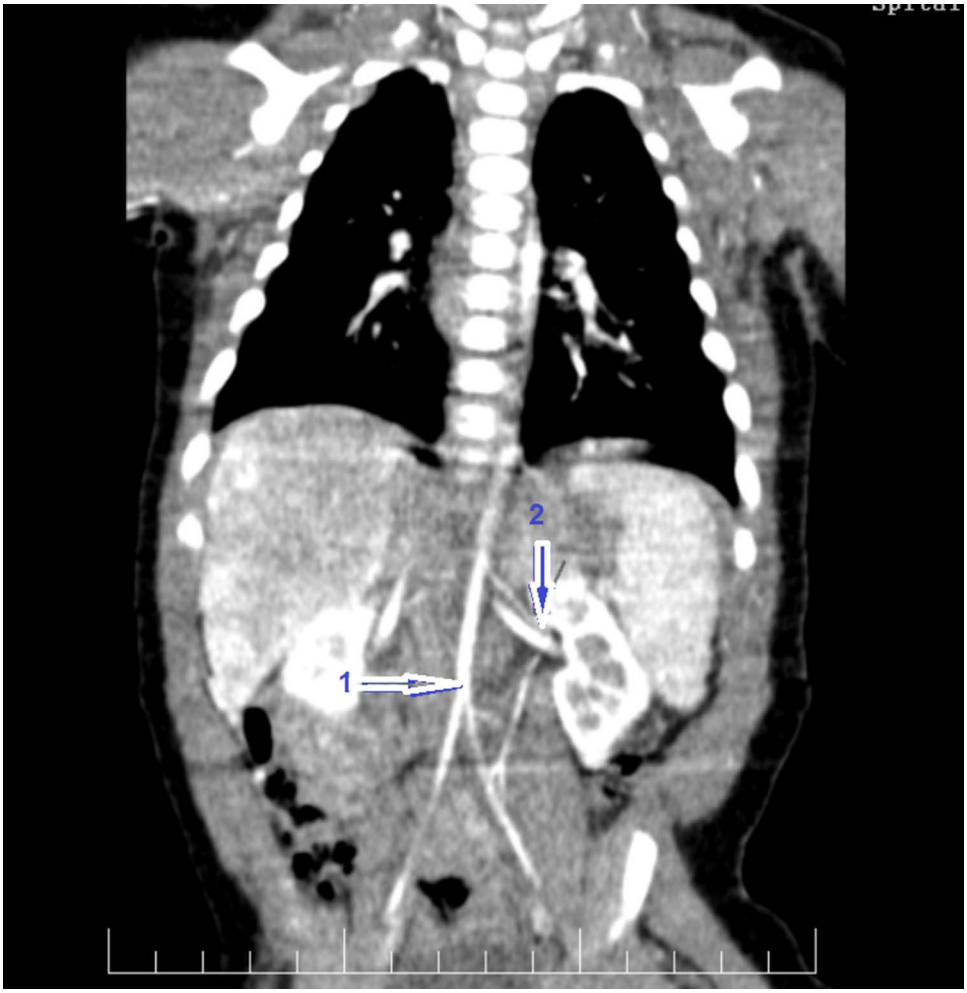

Figure 3 Thoracic and abdominal CT angiogram revealing reduced caliber of the abdominal aorta (*Z* score −3.8) – (arrow 1) and narrowed left renal artery (diameter < 1mm) – (arrow 2) in a 3-month-old boy with WS.

Alagille Syndrome

Alagille syndrome (ALGS) is a rare autosomal dominant, multisystem disorder resulting from mutations in two genes associated with the Notch signaling pathways: *JAGGED1* in most cases and *NOTCH2* in a minority of cases determining abnormal development of the intrahepatic bile ducts.[87–91] Clinical findings consist in bile duct paucity associated with chronic cholestasis, cardiovascular abnormalities typically peripheral pulmonary artery stenosis, skeletal abnormalities (butterfly vertebrae), ophthalmologic anomalies (posterior embryotoxon), renal anomalies, vascular involvement, and characteristic dysmorphic features.[60,92]

ALGS is encountered in 1–8% of MAS cases.[1,3,16] Vascular abnormalities in ALGS include intracranial vascular abnormalities as aneurysm or moyamoya disease, which may lead to intracranial bleeding in up to 15% of cases and represents a major cause of morbidity and mortality in this disorder.[10,90] Other arteries involved are pulmonary arteries, aorta, renal, celiac, mesenteric, subclavian and carotid arteries.[91] MAS was found in 1–2.4% of the individuals diagnosed with ALGS in a large study, but the association between ALGS and MAS is underestimated.[10,90,93] Superior mesenteric artery and celiac trunk are most often involved (Table 5). Median arcuate ligament syndrome was found to be involved in visceral artery stenoses in patients with ALGS.[10]

The association between ALGS and MAS is not incidental. Developmental and molecular studies have been demonstrated *JAG1* and Notch signalling pathway in vascular development and expression of *JAG1* was found in all major arteries during embryogenesis.[6,60,94] Mutations of *JAG1* and Notch regulation signalling defect will determine

defects in angiogenic vascular remodelling and abnormal vessel structure.[61,87,95–97] Aortic coarctation and visceral branches stenosis in ALGS are caused by myo-intimal hyperplasia of the vascular wall.[62]

Whole exome sequencing studies revealed that protein truncating mutations, which usually are associated with other clinical features of ALGS or even missense mutations which may not have additional symptoms of ALGS may result in MAS.[16]

CT angiography and magnetic resonance angiography are used to diagnose MAS in children with ALGS.[63,64,87] Because the vascular disease can be progressive, periodic imaging by ultrasound or angiographic techniques are required.[10]

Treatment of MAS in patients with ALGS includes medical therapy, endovascular and surgical intervention. Invasive procedure can be difficult because of presence of thick and fibrous media of the vessels.[10] Medical treatment was preferred as the only option in 40% of the children with MAS and ALGS and hypertension was controlled in 67% of the cases (Table 5). In 13.3% of the cases, combined interventional therapy was necessary (angioplasty, aortic bypass, TESLA and renal auto-transplant).

Tuberous Sclerosis

Tuberous sclerosis (TS) is a genetic disorder inherited in an autosomal dominant fashion resulting from mutations in the genes *TSC1* and *TSC2* that affect multiple systems: brain, retina, kidneys, heart, skin and vascular. Diagnosis criteria consist in genetic criteria (identification of either *TSC1* or TSC2 pathogenic mutation) and clinical criteria: major features (hypomelanotic macules, angiofibroma, ungual fibromas, Shagreen patch, multiple retinal hamartomas, cortical dysplasia, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis, angiomyolipoma) and minor features ("confetti" skin lesions, dental enamel pits, intraoral fibromas, retinal achromic patch, multiple renal cysts, nonrenal hamartoma).[98,99] Vascular involvement in tuberous sclerosis consists in aneurysm of the aorta, pulmonary artery, intracranial arteries, subclavian and iliofemoral arteries and stenotic-occlusive lesions of the large and medium size arteries, affecting aorta, common iliac artery, renal artery, mesenteric artery, coronary artery and moya-moya disease.[100–104] Abdominal aortic coarctation and renal artery stenosis have been reported most often either in isolation or as components of MAS in four pediatric patients.[11,100]

The pathogenesis of vascular disease in TS is unclear. Dysplastic and degenerative changes within the arterial wall, including fibrocytic and myofibrocytic intimal proliferation and medial hyperplasia, obliterative dysplasia have been described.[101–104]

Whole body or targeted vascular screening by duplex ultrasound, magnetic resonance angiography and CT angiography should be performed in TS patients with hypertension or signs or symptoms attributable to stenotic vascular lesions.[11,105]

Angioplasty represents a useful method of treatment for stenotic lesions in TS.[11]

Although hypertension in TS patients has been classically attributed to the renal parenchymal disease, vascular occlusive or stenotic disease must be considered.

Mucopolysaccharidoses (MPS)

Mucopolysaccharidoses are rare genetic lysosomal storage disorders, autosomal recessive or X-linked inherited caused by alterations in the functional enzymes, which degrade glycosaminoglycans (GAGs). Progressive pathological accumulation of glycosaminoglycans determines dysfunction of most organ-systems to different degrees, leading to a considerable heterogeneity in clinical presentation, both in age of onset of symptoms and severity.[14,106] Somatic involvement includes facial dysmorphism, enlarged liver and spleen, hernia, stiff joints, respiratory infections, recurrent otitis, deafness, cardiac valve disease and neurological impairment.[14,106–110] Cardiac involvement is common in MPS, is present at the early stage of the disease because of thickening of the valves' leaflets and is progressive.[107–109] The most affected valves are the mitral and aortic valves. GAGs infiltration of the myocardium can also be present. Great vessels may be affected by increased wall thickness.[13,107] Diffuse narrowing of the thoracic and abdominal aorta has been reported in three patients with MPS type 1 (one patient with abdominal aorta stenosis and 2 patients with thoraco-abdominal aorta narrowing), in four patients with MPS type I and in one patient with MPS type VII and was correlated with increased arterial pressure.[13–15]

Conclusions

Genetic forms of MAS, although rare, represent an important cause of hypertension in children and should be considered in the differential diagnosis of hypertension in paediatric population with genetic disorders. The extent of vascular disease depends on the type of genetic disorder. MAS determined by genetic disorders is more often associated with suprarenal stenosis and extra-aortic involvement. Management of hypertension can be difficult, and each patient needs individualised therapy. Medical treatment is preferred in children with WS and ALGS and MAS. In terms of clinical practice, we recommend evaluating the children with MAS in detail because they may present other specific manifestations for certain genetic diseases, and on the other hand, it is necessary to detect the presence of MAS in children who were already diagnosed with certain genetic diseases.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki and the patients gave their informed consent for using the results of imaging investigation.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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