Mid-Aortic Syndrome in Williams-Beuren Syndrome with an Atypical Small-Sized Deletion of Chromosome 7q11.23 Misdiagnosed as Takayasu Arteritis

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Summary

Mid-aortic syndrome (MAS) is a rare condition characterized by stenosis of the thoracic and/or abdominal aorta. Williams-Beuren syndrome (WBS) is a relatively rare cause of MAS. We report a case of incidentally diagnosed MAS caused by WBS without typical manifestations caused by an atypical small-sized deletion in chromosome 7q11.23, which was initially misdiagnosed as Takayasu arteritis.

Key words: Hypertension, Aortic diseases

CASE REPORT

A 17-year-old male with hypertension, who was diagnosed at a regular health checkup, visited our hospital. The patient had no unusual medical history, familial history, or symptoms associated with hypertension, such as headache and claudication. On physical examination, blood pressure was 180/100 mmHg, heart rate was 81 bpm, height was 165 cm (6.6th percentile), and body weight was 72 kg (73.4th percentile). No findings suggesting congenital disease, such as murmur or general appearance, were noted.

The patient was admitted for an evaluation of secondary hypertension. Laboratory tests revealed the following: white blood cell count, 8840/μL; hemoglobin, 11.2 g/μL; platelet count, 393 K/μL; blood urea nitrogen, 10.0 mg/dL; creatinine, 0.95 mg/dL; erythrocyte sedimentation rate (ESR), 4 mm/hour (range, 0-10 mm/hour); C-reactive protein (CRP), 1.14 mg/L (range, 0-5 mg/L); 24-hour urine-free cortisol, 36.66 μg/day; 24-hour urine metanephrine, 0.175 mg/day; 24-hour urine vanillylmandelic acid, 2.6 mg/day; plasma renin activity, 4.23 ng/mL/hour; and serum aldosterone, 16.49 ng/dL. Based on laboratory test results, endocrine diseases such as pheochromocytoma, Cushing’s syndrome, and aldosteronism were ruled out.

The difference in systolic blood pressure between the right and left arms was 13 mmHg (right, 149 mmHg; left, 136 mmHg). Ankle brachial index was decreased to approximately 0.70 (right)/0.62 (left). These findings suggested an aortic abnormality. Transthoracic echocardiography (TTE) and computed tomography angiography (CTA) were performed. With TTE, cardiac chamber size and systolic/diastolic function were normal without structural abnormalities. On the other hand, we performed renal artery Doppler ultrasonography to evaluate renovascular hypertension, but there was no evidence of renal artery stenosis and the normal renal arterial resistive index was 0.59 (right)/0.60 (left). However, CTA (Figure 1) revealed a diffusely narrowed thoracoabdominal aorta without involvement of both renal arteries or other major branches. CTA and renal artery Doppler ultrasonography findings with hypertension indicated MAS. Aortography (Figure 2) performed based on CTA results revealed diffuse narrowing of the distal descending thoracic aorta extending as far as the suprarenal abdominal aorta and intact renal arteries.

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Furthermore, the pressure gradient between the proximal descending thoracic aorta and abdominal aorta was 20 mmHg. According to the 1990 American College of Rheumatology (ACR) classification criteria for Takayasu arteritis, the patient presented with three criteria: age at disease onset (< 40 years), systolic blood pressure difference (> 10 mmHg) between arms, and aortographic aortic narrowing. The patient was initially diagnosed with Takayasu arteritis. Therefore, [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography integrated with computed tomography (FDG-PET/CT) was performed to evaluate disease activity. However, FDG-PET/CT (Figure 3) presented no abnormal FDG uptake in the thoracic or abdominal aorta. We focused on the patient’s sex (young male), the observation that all inflammatory markers (e.g., ESR and CRP) were normal, and that there were no systemic symptoms (e.g., fatigue, fever, weight loss).

We performed a chromosomal microarray (CMA) using CytoScan™ DX assays (Santa Clara, CA, USA) with peripheral blood to screen for the presence of any congenital disease that might cause MAS. CMA revealed a 504.3-kb deletion at chromosome 7q11.23 containing ELN, LIMK1, EIF4H, MIR590, LAT2, RFC2, CLIP2, and GTF2IRD1 genes, which was “likely pathogenic” based on Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG guidelines) and a 1.1-Mb duplication at chromosome Yq11.223 containing RBMY1A1, PRY2, PRY, TTTY6, and TTTY5 genes, which was “benign” based on ACMG guidelines. Based on these results, WBS with MAS resulting from atypical small-sized chromosome 7q11.23 deletion was diagnosed.

The patient did not have any clinical indications for surgical correction; thus, medical therapy, including an angiotensin II receptor blocker and a β-blocker, was initiated. After the commencement of treatment, blood pressure was well controlled at 120/70 mmHg and the patient had no symptoms until recently.

**Discussion**

MAS is characterized by narrowing of the mid-aorta between the aortic arch and the iliac bifurcation, often with involvement of renal and visceral branches, causing hypertension, abdominal pain, or claudication. In one study, the etiologies of MAS included idiopathic (61%), aortitis (26%), atherosclerosis (5%), neurocutaneous syndrome (5%), WBS (2%), and other secondary causes (1%).

WBS is a relatively rare congenital and multisystemic condition that occurs in approximately 1 in 10,000 live births.
Figure 2. Aortography. A: Descending thoracic aorta (white arrowheads). B: Suprarenal abdominal aorta (black arrowheads) and both renal arteries (white arrows). Both present diffuse narrowing of the distal descending thoracic aorta and suprarenal abdominal aorta.

Figure 3. [18F]-2-Fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography integrated with computed tomography. A: Maximum-intensity projection image. B: Fusion sagittal view. Both show no abnormal FDG uptake in the thoracoabdominal aorta (black arrowheads).
births.\textsuperscript{12} WBS is typically caused by a 1.5-1.87-Mb deletion containing 26-28 genes on chromosome 7q11.23, the so-called WBS chromosome region (WBSCR). Approximately 2\% of cases of WBS caused by atypical deletion involve the WBSCR.\textsuperscript{3} The diagnosis of WBS usually originates from the clinician’s suspicion. The WBS phenotype substantially varies but generally includes facial dysmorphism (Elfin face), developmental delay (95\%), and cardiovascular abnormalities (86\%).\textsuperscript{7,9} However, WBS due to atypical deletion can display a milder or more complex phenotype than typical deletion.\textsuperscript{8,9}

As the leading factor causing morbidity and mortality in WBS, cardiovascular abnormalities are clinically important and commonly include vascular stenosis, hypertension, and valvular abnormality. Supravalvular aortic stenosis (SVAS) is the most common (35\%-65\%) abnormality.\textsuperscript{10} MAS is a relatively rare but important cardiovascular manifestation of WBS.\textsuperscript{10}

The interesting points of our case include the following. Our patient had mild or no classic manifestations of WBS due to an atypical small-sized deletion. For example, the patient was short in stature, but the 6.6th percentile is not acceptable for short stature diagnosis (< 3rd percentile). Typical facial dysmorphism and SVAS, the most common cardiovascular abnormalities in patients with MAS, were absent. However, MAS and hypertension were clearly observed. Furthermore, the patient had another genetic mutation, the duplication of chromosome Yq 11.223. This duplication is generally known as a benign variant. However, due to the characteristics of the genetic variants that it was difficult to completely predict the phenotype, we could not entirely exclude the possibility that the duplication might affect the atypical phenotypes of WBS. Therefore, the patient was initially misdiagnosed with Takayasu arteritis. This misdiagnosis might be affected by the limitations of the 1990 ACR classification criteria for Takayasu arteritis, making it difficult to distinguish Takayasu arteritis from other vascular diseases. Violetta, et al. previously reported a case of MAS due to WBS, which was firstly misdiagnosed as systemic vasculitis.\textsuperscript{11} However, there are several differences between their case and the present case. For example, our patient was asymptomatic and had no typical facial dysmorphism and structural heart disease suggesting WBS. Furthermore, stenosis of the aorta was much more severe in their case. However, there are some notable similarities between the two cases. In both cases, MAS was initially misdiagnosed as Takayasu arteritis. Moreover, acute phase reactant (APR) (e.g., ESR, CRP) was within normal range, and FDG-PET/CT showed normal uptake on the affected aorta. Therefore, APR and FDG-PET/CT could be a useful diagnostic tool in distinguishing Takayasu arteritis and other vasculopathies such as MAS.

One limitation of the present case report is that we could not evaluate the patient’s intelligence quotient. However, considering our patient was attending high school, mental retardation is unlikely.

To our knowledge, this is the first case of WBS due to incidental identification of MAS caused by an atypical small-sized deletion in chromosome 7q11.23 diagnosed without other typical features. As a cause of MAS, WBS is relatively rare but must be considered as a differential diagnosis.

Disclosure

Conflicts of interest: There are no conflicts of interest to declare.

Informed consent: Written informed consent was obtained from the patient and his mother.

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