Williams-Beuren syndrome – a rare cause of recurrent hemoptysis

Sindromul Williams-Beuren – cauză rară de hemoptizie recurentă

Abstract

Williams-Beuren syndrome (WBS) is a rare genetic disease with a distinctive constellation of clinical findings. The disease can be diagnosed clinically by a recognizable pattern of malformations, including cardiovascular malformations, a characteristic facial dysmorphism, as well as neurological and cognitive features. We present the case of a 23-years-old woman repeatedly admitted to Pulmonology Clinic for massive hemoptysis. Diagnosis of Williams-Beuren syndrome was revealed by clinical findings and confirmed by CT-angiography data of cardiovascular malformations and fluorescence in situ hybridization (FISH) genetic test. WBS is a multisystem disorder and usually is recognized by clinician. If clinical impression is not clearly consistent with WBS, FISH remains the most widely used test.
Keywords: ***Williams-Beuren syndrome, hemoptysis***

Rezumat

Sindromul Williams-Beuren este o boală genetică rară, ce se prezintă printr-o constelație de trăsături clinice distinctive. Boala poate fi recunoscută după pattern-ul de malformații associate, ce include anomalii cardiovasculare, trăsături faciale distincte, profil neurologic și cognitiv particular. Se prezintă cazul unei paciente de 23 ani, nediagnosticată anterior cu sindromul Williams-Beuren (WBS), spitalizată în clinica pneumologie pentru hemoptizii masive repetate. Diagnosticul s-a bazat pe tabloul clinic sugestiv și a fost susținut de confirmarea malformațiilor cardiovasculare prin tomografie computerizată în regim aortoangiografie și testare genetică (hibridizarea fluorescentă in situ). WBS este o afectiune multisistemică, de obicei, recunoscuta de către clinician. Dacă tabloul clinic nu este în mod clar în concordanță cu WBS, hibridizarea fluorescentă in situ rămâne testul genetic cel mai utilizat.
Cuvinte-cheie: ***sindromul Williams-Beuren, hemoptizie***

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Introduction

Williams-Beuren syndrome (WBS) is a rare genetic disease caused by a chromosomal microdeletion in the q11.23 region of one copy of chromosome 7. WBS is characterized by a developmental disorder associating a cardiac malformation (most frequently supravalvular aortic stenosis) in 75% of cases, psychomotor retardation, a characteristic facial dysmorphism and a specific cognitive and behavioural profile. WBS occurs at a frequency of approximately 1 in 7 500 – 10 000 live births[(1)].

Clinical case

A 23-years-old woman was admitted to the Pulmonology Clinic for repeated hemoptysis up to 300 ml with signs of asphyxia and anemia (Hb 7.7 g/l, RBC 2,9 x 10^{12}/ml). Since childhood she was diagnosed with ostium secundum type atrial septal defect (ASD) and a moderate mental retardation. Early developmental features such as sitting and walking were within normal limits. By the age of 4 years she showed a delay in language acquisition as well as difficulties in spatial cognition. Actually she has low-normal height (H 150 cm, M 45 kg, BMI 20) and childlike facial features (Figure 1).

The last 2 years the patient presented rare small hemoptysis, which have been interpreted by clinicians as a manifestation of pulmonary hypertension secondary to ASD. Last year repeated echocardiographic examinations showed a 12 mm ASD, pulmonary artery systolic pressure varying from 42 to 67 mm Hg in various examinations, 32 mm right ventricular cavity and 12 mm wall thickness, 47 mm right atrium cavity.

During hospitalization in a cardiology department for an episode of hemophtysis and arterial hypertension (up to 180/100 mm Hg) an ANCA-associated vasculitis (granulomatosis with polyangiitis) was suspected based on the slightly increased level of antineutrophil cytoplasmic antibodies (3-proteinase level 7,6 U/ml) and imaging findings. The kidneys ultrasound showed normal sizes. Signs of renal arteries stenosis were not detected at Doppler ultrasound. Blood and urine calcium levels were within normal range. At this moment chest X-ray and CT revealed bilateral ground glass opacities in the upper lobes and bilateral nodular opacities in the right S2, S6 and S10 segments and in the left S2 segment (Figures 2A, 2B, 3A, 3B). Corticosteroid therapy (30 mg prednisolone orally) was started. The cyclophosphamide was

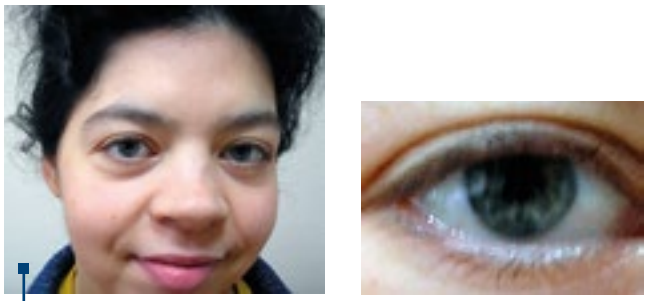

Figure 1. *Facial appearance of the patient: broad forehead, periorbital fullness, "lacey" iris, flat nasal bridge, full cheeks and lips and a wide mouth*

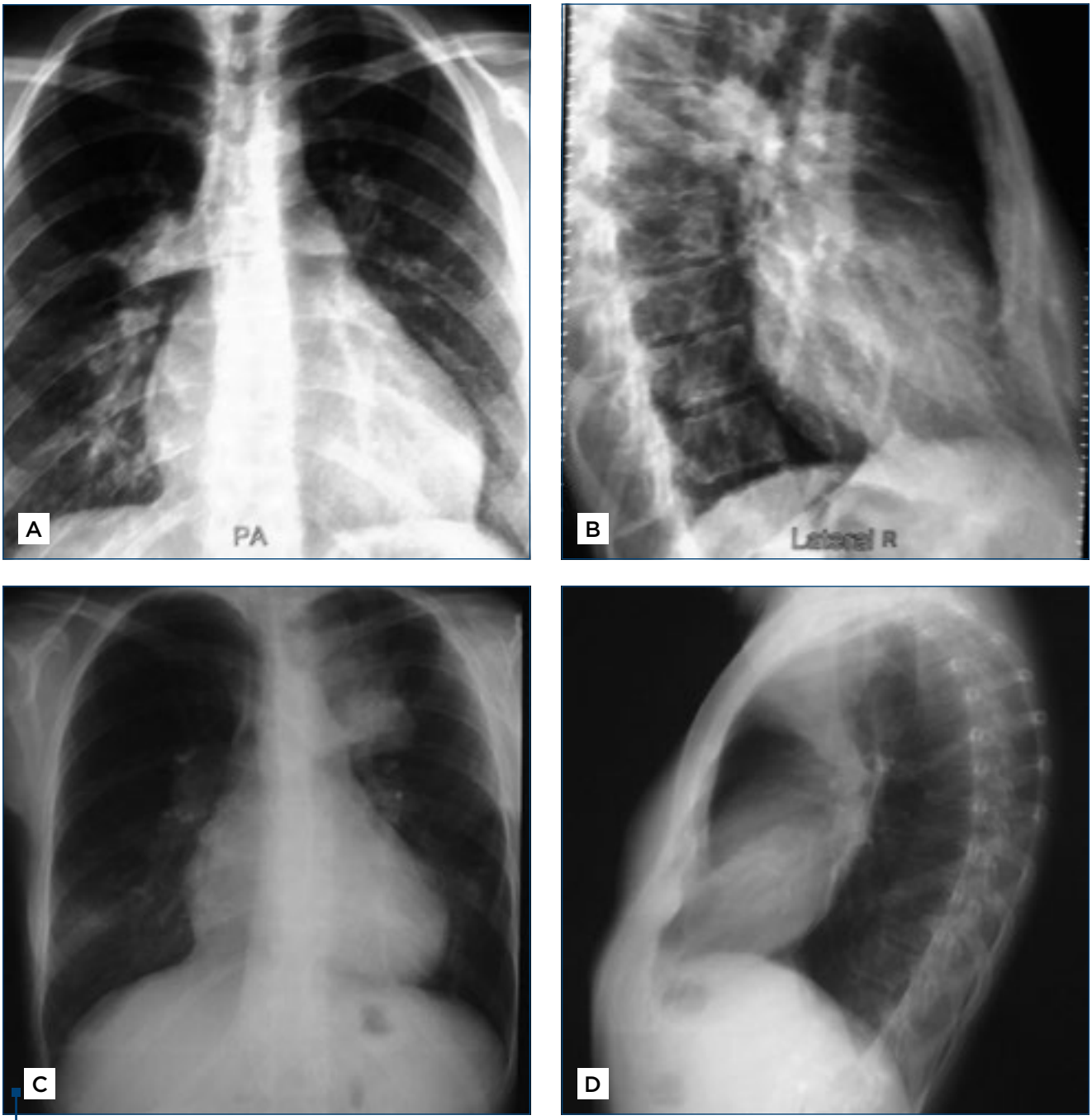

Figure 2. *Chest radiography: A, B in june (2013) bilateral nodular opacities on the right in S2, S6, S10 and in left S2; C, D in january (2014) on the left the opacity extended in S1, S3*

not associated considering the active hepatitis with mixed viral hepatic viruses (hepatic viruses HBV and HCV).

After another episode of massive hemoptysis (400 ml) 3 months later the patient was admitted to pulmonology department. Thoracic CT revealed on the left the enlargement of the opacity to S3, without clear borders, 2,7 cm in diameter (Figure 3C, 3D). Bronchoscopy showed compression of the 4-th and 5-th segmental bronchi with bleeding from S3 bronchus. The transbronchial lung biopsy did not succeed. Bronchial mucosa biopsy was with no atypical cells or any kind of inflammation. Tests for *Mycobacteria tuberculosis* (sputum smear, Gene X-pert, liquid and solid media cultures) were negative in the bronchial washings as well as in the sputum. Nasal mucosa biopsy did not confirm granulomatous necrotizing vasculitis.

The diagnosis of systemic vasculitis was rejected based on serology tests and biopsy and the corticosteroid therapy was stopped. The assumption of lung tumor was not confirmed, the open lung biopsy was refused by patient.

On the 6 months follow-up the left upper lobe opacity progressed to 61 x 54 mm with S3 atelectasis (Figures 2C, 2D, 3E, 3F). The imagist's suggestion was of a conglomerate of granulomatous peribronhovascular consolidations.

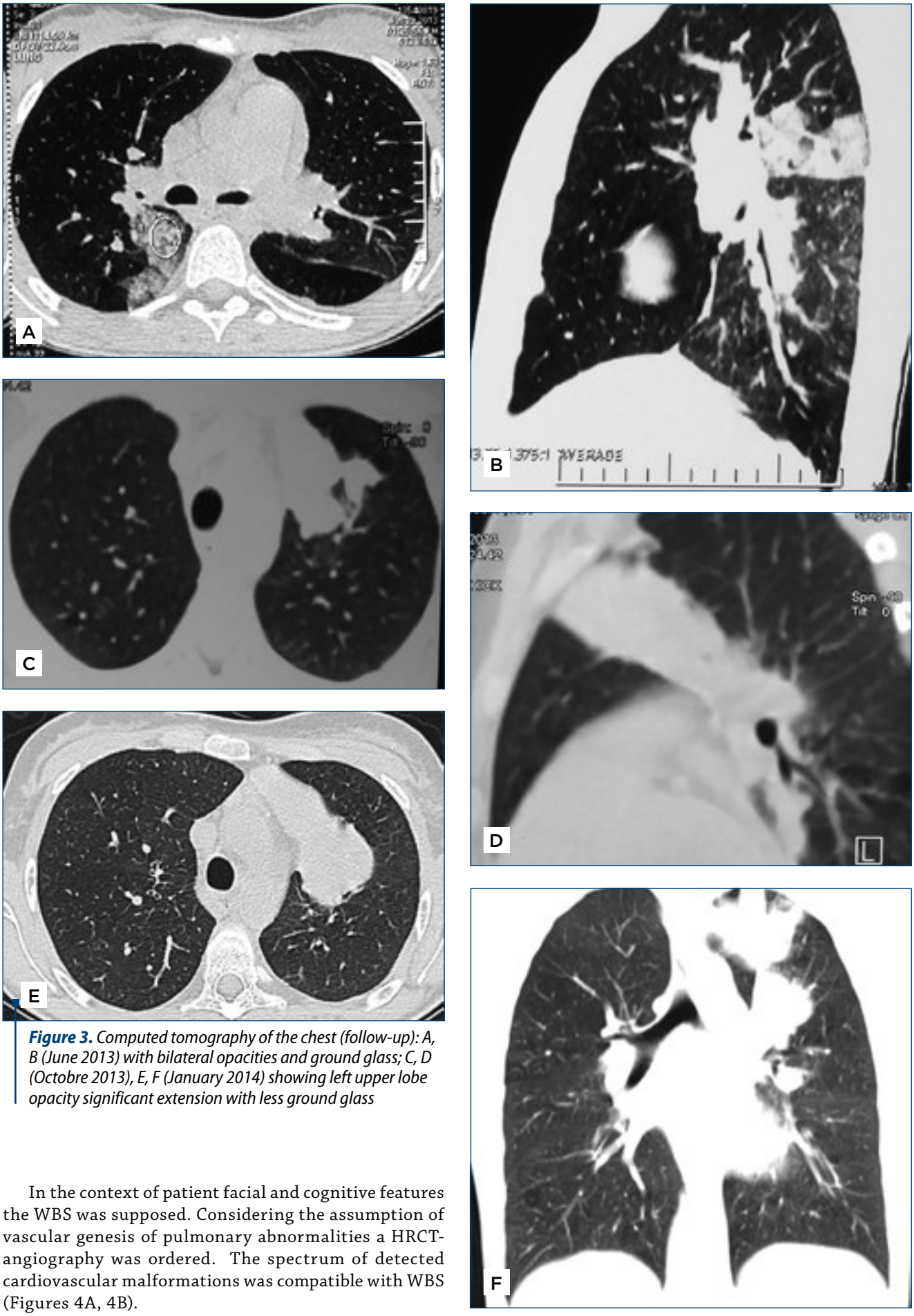

Figure 3. *Computed tomography of the chest (follow-up): A, B (June 2013) with bilateral opacities and ground glass; C, D (Octobre 2013), E, F (January 2014) showing left upper lobe opacity significant extension with less ground glass*

In the context of patient facial and cognitive features the WBS was supposed. Considering the assumption of vascular genesis of pulmonary abnormalities a HRCT-angiography was ordered. The spectrum of detected cardiovascular malformations was compatible with WBS (Figures 4A, 4B).

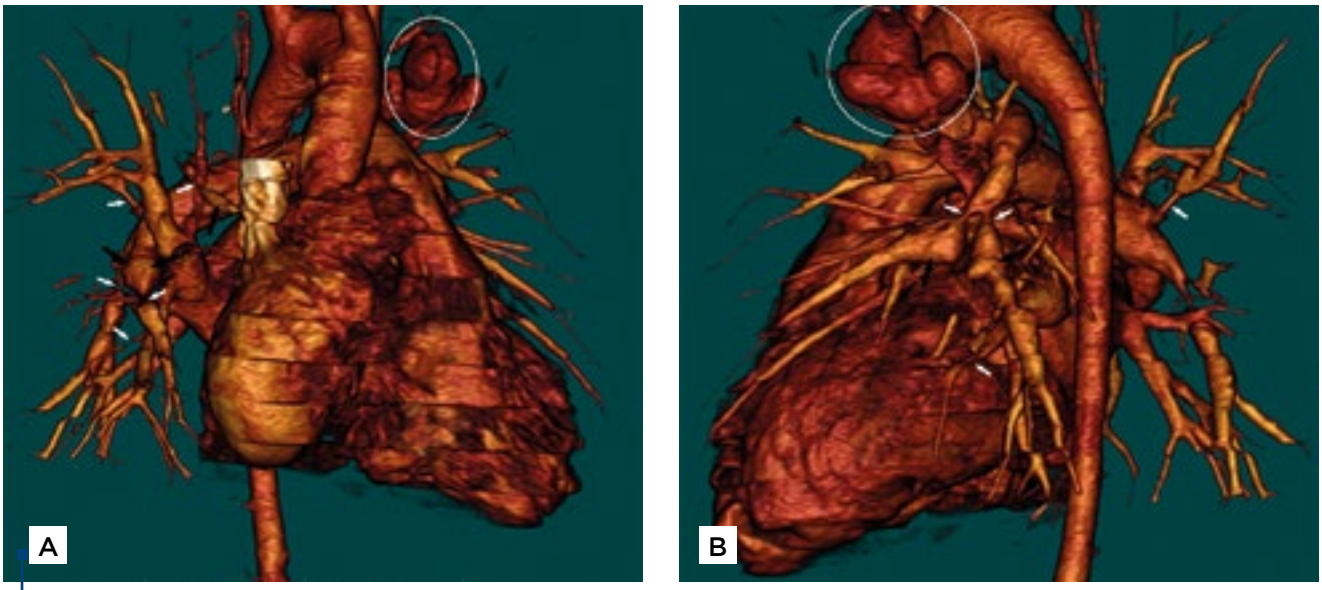

Figure 4. *CT- angiography of the chest (cardiovascular reconstruction) showing left apical poststenotic aneurysm (circles), multiple pulmonary arteries stenoses with poststenotic dilatation (some pointed with arrows)*

The atrial septal defect (14 x 10 mm), pulmonary hypertension and right ventricular hypertrophy (12 mm wall) and normal left ventricular thickening was confirmed. The aortic stenosis was not revealed, but the hypoplastic descending aorta was found. The important segmental stenoses (95% of lumen) of the left subclavian artery and several segmental pulmonary arteries stenoses (75-95%), up to 15 mm length, with poststenotic aneurysmal dilatation were detected.

On the left was found a critical apical artery stenosis, more than 95% of lumen over a length of 8 mm, with a poststenotic aneurysm (34 mm in diameter) and perianeurysmatic hematoma with leakage of contrast at this level (32x35 mm). This hematoma caused lung atelectasis by compression.

Brachiocephalic trunk, the common carotid artery, subclavian artery, right vertebral artery, pulmonary trunk and its main branches up to right and left lobar arteries did not present abnormalities. The pulmonary veins, cava veins were without abnormalities.

The FISH test confirmed the microdeletion of elastin (ELN) and LIM domain kinase 1 genes (LIMK1) in the 7q11.23 region.

Discussions

In 1961, Williams described a syndrome characterized by supravalvular aortic stenosis (SVAS), mental retardation and distinctive facial features[2]. Beuren (1962) described a similar syndrome with the additional features of dental anomalies and peripheral pulmonary artery stenosis[3]. Now these phenotypes are referred to the same disorder, Williams-Beuren syndrome. Full-blown WBS includes SVAS, multiple peripheral pulmonary arterial stenoses, "elfin face" and developmental delay with mental and statural deficiency, characteristic dental malformation and infantile hypercalcemia.

WBS is caused by a hemizygous contiguous gene deletion of 1.5 to 1.8 Mb on chromosome 7q11.23, which contains approximately 28 genes. The chromosome 7 microdeletion occurs because of the unique genetic architecture in this region. The deleted region is flanked by homologous clusters of genes and pseudogenes organized into duplicons (a low-copy-repeat block) with a high proximity to each other. In meiosis during gamete formation the region can be deleted if unequal crossing over arises. In the most cases deletion is sporadic and then healthy parents do not carry the deletion. The most breaks occur in the medial and centromeric duplicons, with the deletion of 1,5 to 1,8 million base pairs encoding 26 to 28 genes. Hypoexpression of deleted genes products leads to considerable variation in the clinical manifestations of this syndrome. The loss of the ELN gene allele produces the cardiovascular pathology of WBS. Stenosis of medium and large arteries constitutes the prototypical cardiovascular abnormality of WBS. Arterial narrowing (ranging from discrete narrowing to multiple stenotic areas or, occasionally, even diffuse hypoplasia) may be isolated or may occur simultaneously in numerous locations, including the aortic arch, the descending aorta, the pulmonary, coronary, renal, mesenteric, intracranial arteries[4].

The phenotypic consequences of losing other alleles within the WBS chromosome region are much less clear. Earlier some abnormalities of the connective tissue were also attributed to ELN hemizygosity: premature aging of skin, hoarse voice, periorbital puffiness, inguinal herniae and diverticula of colon and bladder. However, the reports of SVAS patients with ELN deletions and normal facial features suggest that other genes than ELN are contributors to these clinical findings.

About 2% of WBS patients have atypical deletion. An "atypical" WBS individual has a smaller genetic deletion, usually of extratelomeric genes and presents milder features of disease.

Despite genetic advances, the considerable phenotypic variability of WBS patients remains less explained. The polymorphisms of disease is also determined by the nondeleted copies of genes, expression level, variable effects of the deletion on the expression of neighboring genes, the effects of modifier genes, epigenetic alterations. Currently there is no genetic test that predicts the severity of the WBS phenotype[4,5].

WBS is a multisystem disorder with a characteristic constellation of clinical findings and usually is recognized by clinician. If clinical impression is not clearly consistent with WBS, FISH remains the most widely used test. The diagnosis can also be confirmed by microsatellite marker analyses, multiplex ligation-dependent probe amplification, quantitative polymerase-chain-reaction assay, array comparative genomic hybridization.

Common ***cardiovascular*** findings of WBS are SVAS, aortic hypoplasia and coarctation of the aorta, multiple peripheral pulmonary stenoses, mitral valve prolaps, bicuspid aortic valve. The severity of SVAS ranges from discrete to severe and is found in approximately 70% of patients. Rarely patients have "middle aortic syndrome" with narrowed the thoracic and abdominal aorta and branches. An increased carotid artery intima media thickness is present in all cases.

Intracardiac lesions such as ventricular or atrial septal defects are uncommon, whereas myxomatous degeneration of aortic or mitral-valve leaflets occur in up to 20% of patients. Left-sided stenoses remain stable, but obstruction can progress during the first 5 years of life. Patients with aortic hypoplasia and surgery for SVAS developed restenosis, whereas patients without aortic hypoplasia remained free of restenosis. Obstruction of right ventricular outflow, particularly peripheral pulmonary stenoses, often resolves spontaneously[4,5].

Pulmonary artery stenosis is the second most common cardiovascular abnormality in WBS, with an incidence ranging from 37% to 75%. Stenosis can be discrete or diffuse involving large segments of the pulmonary arterial tree, most commonly occuring in the branch and peripheral pulmonary arteries. Supravalvar pulmonary stenosis is less common. Pulmonary artery stenosis is more common in patients in the first year of life, with a natural improvement as the patient grows. Pulmonary arterial concentrations of elastin normally decrease in the first few months of life (time when pulmonary vascular resistance is normalizing) and this fact theoretically decreases the role of elastin in development of the arterial stenoses[6].

Pulmonary arterial aneurysms may develop following pulmonary balloon angioplasty and rarely are spontaneous in patients with WBS[6,7]. Spontaneous rupture is considered a rare complication of pulmonary artery aneurysm in WBS, therefore in our case the diagnosis of WBS in an adult with repeated massive hemoptysis was unexpected.

Cardiovascular complications are the major cause of death in patients with WBS[4,5].

The ***facial features*** range from subtle to dramatic. The typical facial appearance termed "elfin facies" consists of broad forehead, medial eyebrow flare, periorbital fullness, strabismus or esotropia, stellate iris pattern, flat nasal bridge, short upturned nose, malar flattening, full cheeks and lips, a long smooth philtrum, a delicate pointed chin and a wide mouth. The face becomes more coarse with age, minor facial anomalies being attenuated with time. Typical features do not correlate with mental status. In a series of cases ascertained through SVAS were found patients with mental retardation without "elfin facies" and patients with "elfin facies" who were mentally normal, thus was suggested that the term "elfin facies" be dropped[8].

The ***iris pattern*** described as "lacey" (by others as "stellate") can be a useful diagnostic clue in infants. A stellate pattern was noted in the irides of 51% - 77% of the WBS patients. This pattern is more difficult to detect or is absent in heavily pigmented irides. In patients with brown irides can be present whitish anomalies. Another ocular abnormalities on funduscopy is retinal vascular tortuosity[10,11].

In a MRI study in WBS patients no consistent ***cerebral abnormalities*** were detected[12]. Narrowing of the cerebral arteries can cause strokes with brain damage and chronic hemiparesis in children, increased irritability, loss of consciousness and seizures.

Patients with WBS have common ***neurodevelopmental features.*** The IQ in patients with WBS varies from 20 to 106, the mean 58 demonstrates a mild-to-moderate intellectual disability. However cognition in WBS is more complex than indicated by IQ alone. Specific cognitive deficits include poor visual-motor integration. As a result, affected individuals have problems visualizing a complete picture but instead see only the parts. Patients with Williams syndrome are hypersensitive to sounds. The most frequent sounds of daily life to which the children are sensitive included electric machines, thunder, bursting balloons, and fireworks. The children respond with marked fear and exhibited aversive behaviors. Affected individuals also suffer from attention deficit disorder. Language development, by contrast, is relatively spared and some elements of speech may be enhanced, particularly the quantity and quality of vocabulary, auditory memory, and social use of language. Many patients sing or play musical instruments with considerable expertise and they rarely forget a name. They tend to be empathetic, loquacious, and sociable. Because of their engaging personalities and language skills, mental retardation is often underestimated in children with WBS. In spite of the friendly personality of patients, many are socially isolated, present anxiety and phobic disorder, attention deficit–hyperactivity disorder[13,14].

Skeletal development is approximately normal in both sexes. In about 1/3 of children with WBS was described intrauterine growth retardation and poor growth during the first 2 years of life. After delayed growth in the first years of life, catch-up growth

occurred with the ultimate attainment of low-normal adult height. A pubertal growth and menarche occur with 1 to 2 years earlier than normal[15].

A common manifestation of WBS is the limitation of supination at the elbow with radioulnar synostosis, pectus excavatum, hypoplastic nails, and hallux valgus, cleft lip with or without cleft palate. Were pointed the myopathy rise to hypotonia in infancy, delayed walking, joint contractures, scoliosis, and increased exhaustion on exertion.

Patients with WBS have a harsh, brassy or hoarse voice due to cord dysfunction caused by abnormal vocal cord elastin. In some severe cases with bilateral vocal cord paralysis, patient required tracheostomy. Other signs attributable to connective tissue abnormalities are inguinal hernia, unilateral renal agenesis.

Among ***endocrine abnormalities*** associated with WBS can be noted hypercalcemia, diabetes mellitus and subclinical hypothyroidism. The prevalence of impaired glucose tolerance is high among patients with WBS.

One or more episodes of hypercalcemia were reported in 5% to 50% of patients with WBS. Hypercalcemia is generally mild, though it can be moderate or severe, particularly during infancy. The episode of hypercalcemia can be asymptomatic or associated with nonspecific symptoms (colic, irritability, hypotonia, diminished appetite, constipation). Hypercalciuria generally accompanies hypercalcemia. Isolated hypercalciuria can occur. Nephrocalcinosis is relatively rare. Various mechanisms have been suggested to cause hypercalcemia: vitamin D sensitivity, increased 1,25-dihydroxyvitamin D levels and defective calcitonin synthesis or release. People with WBS should avoid taking extra calcium and vitamin D[4,5].

Typical ***renal abnormalities*** are renal artery stenosis, unilateral or bilateral, nephrocalcinosis, renal cystic dysplasia, asymmetry in kidney size, small kidneys, solitary kidney, and pelvic kidney. Recurrent urinary tract infections occur in WBS patients with urethral stenosis and bladder diverticula, vesicoureteral reflux. Persistent hypertension is not correlate with renal artery status, but hypercalcemia was strongly associated with the presence of hypertension[16].

Gastrointestinal problems includ chronic constipation and diverticulosis.

Treatment of WBS patients includes a combination of medical monitoring, anticipatory guidance, direct therapies, pharmacotherapy, surgery, and adaptive changes. None of the available treatments are curative. Treatment involves easing the symptoms connected to the syndrome.

Vascular malformations require regular follow-up as well as dedicated management. For this reason, children affected by WBS should be managed by a paediatric cardiology team with knowledge of this pathology. Narrowed blood vessels can be treated if they cause symptoms. Surgery is the preferred approach for repair of discrete moderate-to-severe aortic stenoses. Less invasive procedures such as balloon angioplasty and stent insertion have been successful but carry a higher risk of rupture, aneurysm, or restenosis, as might be expected given the characteristic overgrowth of vascular smooth muscle. The decision for surgical repair of renal artery stenosis must take into account the global involvement of the vascular walls in this pathology. The pulmonary arteries have less smooth muscle and are candidates for angioplasty, but pulmonary-artery lesions in patients with WBS, particularly in the absence of supravalvular aortic stenosis, can often be monitored, since many resolve spontaneously.

The management of arterial hypertension requires a combination of pharmaceutical treatment with a healthy diet and lifestyle. To date, there have been no systematic studies identifying optimal medication to treat hypertension in WBS, so treatment has been individualized. Hypercalcaemia is treated by a calcium-restricted diet. Arterial tension and renal function require life-long surveillance.

Conclusions

Cardiovascular malformations should be considered in the differential diagnosis of causes of pulmonary bleeding. The positive clinical diagnosis of WBS, a rare genetic disorder, should be supported by a multidisciplinary assessment (cardiologist, ophthalmologist, ENT, neurologist, psychologist, genetics). In the presented case, the CT-angiography of the chest have an important role in the diagnosis of distinctive pattern of cardiovascular malformation of WBS. ■

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