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Parkes Weber Syndrome

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Abstract

Introduction: Parkes Weber Syndrome (PWS) is a traditional eponymous denomination of a certain type of angiodysplasia. It is a congenital vascular disease which consists of capillary malformation (CM), venous malformation (VM), lymphatic malformation (LM), congenital arteriovenous malformation (AVM) and multiple arteriovenous fistulas (AVFs). There is a soft-tissue and skeletal hypertrophy of the affected extremity (usually a lower extremity). Moreover the affected limb is warmer and longer than the other side.

Objective: The aim of this article is to summarize the current state of knowledge about Parkes Weber Syndrome: the pathophysiology, genetic inheritance, the main symptoms, the

diagnosis especially differential diagnosis and the current treatment.

Brief descriptions of the state of knowledge: Despite many years, physicians still have difficulties with diagnosing PWS correctly. Although the aetiology is unknown, it is claimed that PWS is caused by mutations of the RASA1, gene located on chromosome 5q13.1, which are inherited in an autosomal dominant manner. This gene is responsible for mediating cellular growth, differentiation and proliferation. No efficacious pharmacological treatment has been found. Nowadays Tranexamic Acid, Sirolimus, Everolimus and Miconazole are used in medical practice. The most frequently utilized invasive treatment methods are amputation, surgical AVM resection and occasionally stent-graft implantation. Furthermore it is thought that embolization, alone or combined with surgical resection leads to clinical improvement.

Summary: Despite the existence of many clinical trials, long term observations and scientific speculations, PWS can still be challenging for clinicians. There is a need for further scientific, molecular and genetic research to diagnose this phenomenon correctly, because despite fact, that its symptoms are similar to other syndromes or entities, therapeutic strategies differ significantly. It is important to increase the awareness of inheritance in an autosomal dominant manner in generation of patients with PWS.

Keywords: Parkes Weber syndrome, PWS, Klippel-Trenaunay syndrome, congenital vascular malformation, arteriovenous malformation

Introduction

Parkes-Weber syndrome is defined by the presence of a capillary vascular malformation with high-flow arteriovenous malformation and multiple arteriovenous fistulas (AVFs) in association with soft-tissue and skeletal hypertrophy of the affected extremity (usually a lower extremity). [1,3,5] Moreover the affected extremity is warmer and longer than the second one, a bruit or thrill may also be detected. [3,6] Incidence is unknown but men and women are affected equally. [3] It is claimed that PWS is caused by mutations of the RASA1, gene on chromosome 5q13.1, which are inherited in an autosomal dominant manner. This gene is responsible for mediating cellular growth, differentiation and proliferation (through the tyrosine kinase pathway). [2,4,6] Although PWS is a clinically distinctive entity, it is still

frequently misdiagnosed as Klippel–Trenaunay syndrome (KTS). Moreover both Parkes Weber and KTS have CM, VM, LM but PWS has in addition AVM, which is very substantial during planning a treatment strategy. [1,3,4,5] The prognosis of PWS is more problematic than in KTS. The main complications and the most dangerous are heart failure, cardiac enlargement, cutaneous ischemia and limb amputation. [1,2]

The main concept of the treatment is to slow: the progression of PWS, heart failure, limb hypertrophy and development of varicose veins as soon as practically possible. Unfortunately, no efficacious pharmacological treatment has been found. What is more, the use of compression garments (e.g. compression stockings) can reduce oedema, improve increasing blood flow and minimalize pain and swelling. [1,4,6] The current results show that the most frequently utilized invasive treatments are amputation, surgical AVM resection and occasionally stent-graft implantation. Furthermore, it is thought that embolization, alone or combined with surgical resection leads to clinical improvement. [1]

History

Parkes Weber syndrome (PWS) was first described by Frederick Parkes Weber in 1907. Parkes Weber described patients with capill venous malformations or ary enlargement of a limb, enlarged veins and arteries in numerous scientific articles. Research conducted by Eerola et al. in 2002 and 2003 proved that Parkes Weber syndrome is a family disease. In addition, this fact was confirmed by research carried out by Revencu et al. in 2008. They demonstrated that this phenomenon is caused by RASA1 gene mutations, as well as many fast-flow vascular malformations. [2]

Epidemiology

Numerous studies prove that the cause of the disease is a genetic mutation. In addition, the mutation can be inherited or may arise *de novo* [7]. About 70% of affected of PWS individuals have an affected parent, while about 30% have a de novo pathogenic variant. Numerous studies prove that RASA1-related disorders are inherited in an autosomal dominant manner. In this connection each child with a mutation in RASA-1 has 50% risk of inheriting the pathogenic variant. Nevertheless, genetic diagnosis before implantation is possible, as well as prenatal diagnosis for pregnant women. If the pathogenic version of RASA1 has been recognized in an affected family member. Limb hyperplasia has been reported in both lower

and upper limbs in RASA1-related disorders. Hypertrophy is usually noticeable in infancy. What is more observations shows that this process can have varying level of severity. [8] Moreover, detailed diagnosis is clinically important, because patients with Parkes Weber syndrome are at risk of cardiac overload, ulceration, and even cardiac failure. [7]

The table 1 contains data for Parkes Weber syndrome until 2016. 36 publications were included, including 48 patients. [1]

Table 1

Patients characteristics	**Numerical data**
The median age of patients	23 years (IQR, 8–32)
PWS and high-output heart failure	31.3%
Gender predominance	female-male ratio: 50%:50%
Chronic venous ulcerations of the affected limb	25.0%
Distal arterial ischemia	8.3%
Lower extremity was affected	87.5%
Upper extremity was affected	12.5%
Spinal arteriovenous malformations	12.5%
Coexistence of aneurysmatic disease	10.4%

Etiology and pathophysiology

Pathophysiology has not been well established and the mechanisms of pathogenesis are also unclear, although there are many theories described in the literature, such as congenital obstruction of the deep veins pertaining to the involved limb [9], mesodermal anomalies resulting in poor formation of vascular and soft tissues during fetal period and finally mutations of genes that determine growth and cellular differentiation, combined with defects of the 5q chromosome (CMC1 locus), which is vital to angiogenesis. [2] There are also newer studies that show that PWS is caused by mutations of the RASA1 gene. The RASA1 gene encodes the p120-RasGAP protein. It is responsible for promoting signaling for varied growth factor receptors that control migration, proliferation and survival of respective cell types, including vascular endothelial cells. [2] In patients with Parkes Weber syndrome were identified the heterozygous loss-of-function RASA1 mutations. Mutations in the RASA1 gene induce production of nonfunctional version of the p120-RasGAP protein. This results in formation of arteriovenous micro fistulas, capillary blush on extremity and bony and soft

tissue hypertrophy. Parkes Weber syndrome has been shown to cover the phenotypic spectrum of capillary malformations - an arteriovenous defect.

Symptoms

PWS usually affects a single extremity, although multiple locations have been described. Most of the patients have lower limb involvement. Early clinical signs include a geographic stain over a limb. In addition, the skin may appear hyperpigmented and varicose veins or even microcystic lymphatic malformations may be present. It is important to note that limb hypertrophy is associated with longitudinal growth, which is a sign of bone involvement and on the other hand, peripheral growth as a sign of soft tissue involvement. Patients with AVFs have a greater degree of hypertrophy. Sciatic nerve enlargement, optic nerve variant, vesicoureteral reflux, colonic involvement and hemimegalencephaly associated with PWS have been described. [11-15] AVFs are the clinical hallmark of PWS. The affected extremity is warmer and longer than the other one, and a bruit or thrill may be explored. Digital closure of an artery proximal to an AVF may lead to bradycardia. This phenomenon is called Branham's sign and it may be present in PWS. Cardiac changes include compensatory tachycardia, increased blood pressure and hypertrophy of the right and then left cardiac chambers. The hypertrophy occurs as a result of hyperkinetic circulation. The degree of hypertrophy depends on the size and number of AVFs, resulting in lymphedema, distal skin alterations secondary to ischemic steal syndrome, and pain, all of which start during childhood. Ulceration associated with AVMs is secondary to blood steal by the hyperactive AVM nidus. Venous dilatation in PWS patients is secondary to epherent hyperflow from the nidus and not secondary to venous valve incompetence. The deformity tends to progress slowly over time, showing a significant longitudinal growth, until the epiphysis is closed. However, pain and fatigue are the most common clinical manifestations. PWS is associated with pulmonary manifestations such as thromboembolic phenomena, pulmonary venous varicosities and pulmonary lymphatic obstruction. [1] In the literature there are also reports about rare cases with hydronephrosis and Kasabach-Merritt coagulopathy. [16]

Diagnosis

Diagnosis of the Parkes Weber syndrome is usually based on clinical symptoms. [1,2,6,8,17] A combination of a cutaneous capillary–lymphatic-VM with AVMs (as main defect) defines the syndrome. Ankle–brachial index assessment should compliment physical examination of

the lower extremity because of the distal arterial ischemia of the affected limb. [1] Imaging techniques are necessary to reveal type, location and extent of the AV lesions. The gold standard is contrast arteriography. [5] It is usually reserved for patients who are potential candidates for embolization. [1,5] Digital Subtraction Angiography (DSA) is the gold standard for the precise separation of high-flow and low-flow vascular malformations. [5] Rapid contrast opacification of the draining veins is typically seen on all angiographic imaging examinations. [2] Magnetic resonance imaging (MRI) is the basis for imaging overgrowth syndromes involving the limbs. MRI is important to assess the deep lymphatic, venous and adipose components in the affected extremity. [2] In MR imaging of high-flow vascular malformations, the main feature on spin-echo sequences are flow-voids. [5] On MRI (T1 and T2 weighted images), signal voids are seen in the vessels with a high flow - arteries, arteriovenous shunts and other veins depending on the degree of the blood flow. [2] In T2 weighted and post gadolinium sequences often show irregular increased signal in some of the muscles. They may have local arteriovenous (AV) shunts, increased subcutaneous fat and lymphedema. [2] The results present that MRPA (MR projection angiography) may detect arteriovenous shunting non-invasively and this distinguish Parkes Weber from Klippel-Trenaunay syndrome. Grey scale and Doppler US are non-invasive methods to distinguish extracranial high-flow from low-flow vascular malformations. [5] On the basis of the results of imaging examinations, treatment is planned. [1]

Parkes Weber syndrome is caused by RASA1 gene mutations. First the analysis of the sequence of RASA-1 is performed. Detected variants are benign, likely benign, of uncertain significance, likely pathogenic or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants. Typically, exon or whole-gene deletions/duplications are not detected. Then gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA) and a gene-targeted microarray designed to detect single-exon deletions or duplications. [8]

The clinical manifestations of RASA1-related disorders [8]

- Capillary Malformations (CM)
- Arteriovenous Malformations / Arteriovenous Fistulas (AVMs/AVFs)
- Parkes Weber syndrome

- Cardiac overload/failure
- Lymphatic malformations
- Tumors (e.g., optic glioma, lipoma, superficial basal cell carcinoma, angiolipoma, nonsmall-cell lung cancer, and vestibular schwannoma)

Table 2 Disorders to Consider in the Differential Diagnosis of RASA1-Related Disorders [8]

Disorder	**Gene(s)**
Hereditary hemorrhagic telangiectasia	ACVRL ENG GDF2 SMAD
Sturge Weber syndrome	GNAQ
Klippel-Trenaunay-Weber syndrome	PIK3CA
PTEN hamartoma tumore syndrome	PTEN
Multiple cutaneous and mucosal venous malformations	TEK
Hereditary glomuvenous malformations (GVM)	GLMN
Hereditary benign telangiectasia	Unknown

Differential diagnosis of Parkes Weber syndrome: [2]

- Klippel–Trenaunay syndrome,
- extensive infantile hemangioma with arteriovenous shunting,
- rapidly involuting congenital hemangioma (RICH)
- noninvoluting congenital hemangioma (NICH)
- Proteus sydrome

Parkes Weber syndrome is often misdiagnosed as Klippel–Trenaunay syndrome. The main differences between syndromes are presented in Table 2.

Table 3 Comparison of Klippel–Trenaunay syndrome and Parkes Weber syndrome [2,5,18]

	Klippel–Trenaunay syndrome	**Parkes Weber syndrome**
Types of vascular malformation	Slow flow capillary, lymphatic, venous	Fast flow capillary, arterial, venous
Colour of cutaneous malformation	Bluish to purplish, localized	Pinkish to red, diffuse
Arteriovenous fistulas	Insignificant	Significant
Lateral venous anomaly	Very common	Not found
Venous flares	Present	Not found
Lymphatic vesicle	Present	Not found
Limb involved *Upper* *Lower*	 5% 95%	 23% 77%
Limb enlargement	Usually disproportionate Soft tissues, bone Macrodactyly (toes),common	arm/leg length discrepancy
Prognosis	Usually good Pulmonary embolism (10% children) Postoperative risk of embolism	More problematic (fistulas) Heart failure Cardiac enlargement Cutaneous ischemia Limb amputation
Bone alteration	Rarefied, osteoporosis	Rarefied, osteoporosis
Brain involvement	Not reported	Intracranial AVM or AVF
Spinal vascular disorders	None	Extradural and spinal AVM
Involved gene mutation	AGGF1, PIK3CA	RASA1

Treatment

There is no effective pharmacotherapy yet. The primary goal should be to improve the quality of patient's life and reduce the risk of complications . The treatment is symptomatic and should be individualized according to the age and clinical features. [6] The most common

invasive treatment methods are: embotherapy followed by amputation and surgical AVM resection. Occasionally stent-graft implantation can be performed.

The absolute indications for invasive treatment of vascular malformation include: [1]

- hemorrhage,
- distal ischemia,
- refractory ulcers,
- high-output heart failure.

Relative indications for invasive treatment include: [1]

- chronic pain,
- claudication,
- functional impairment,
- limb asymmetry,
- cosmetic reasons.

Embolization is the most commonly used procedure in patients with PWS leading to clinical improvement of the limb pain and ischemia, high-output heart failure, myelopathy (related to concomitant spinal AVM) and nonsurgical patients with multiple and deep arteriovenous fistulae. [1,6] Most patients may need a multiple embolization session. [2] Extremity amputation may happen due to distal arterial ischemia, high-output heart failure. [1] Patients with high-output heart failure, recurrent venous ulcerations, chronic pain and arterial aneurysm can be treated by surgical AVM resection. Surgical resection can also be combined with preoperative embolization, minimizing bleeding during surgery. [1] Compression stockings can be helpful to reduce edema and to improve blood flow in order to heal venous ulcerations. [1] Compression garment therapy can be started at 3 months of age. [6]

Summary

Diagnosing a rare and genetic disease is often very challenging. Patients with Parkes Weber syndrome need multidisciplinary medical care. They need the consultations from dermatologists, general surgeons, plastic surgeons, vascular surgeons, orthopedists, interventional radiologists, cardiologists. The prognosis is very problematic and depends on clinical symptoms, numbers of complications and treatment used.

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