



STURGE WEBER SYNDROME, CLASSIC TRIAD FROM A GENETIC, MOLECULAR AND PATHOPHYSIOLOGICAL APPROACH

SÍNDROME DE STURGE WEBER, TRIADA CLÁSICA DESDE UN ENFOQUE GENÉTICO, MOLECULAR Y FISIOPATOLÓGICO

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ABSTRACT

Sturge Weber syndrome (SSW) is characterized by the classic involvement of sporadic neuro-oculocutaneous vascular malformations, the pathophysiology of which to date has not been fully elucidated. The discovery of both an arterial and venous molecular profile in the endothelium present in vascular malformations, together with vascular atresia zones distal to the ectatic zones, have led to questioning the embryological theories put forward for decades, to explore the molecular and genetic characteristics in the affected tissue.

Currently, a high prevalence of somatic mutation in the GNAQ gene has been reported in the affected tissues of patients with SSW, which encodes an alpha subunit of a Gq protein, whose signaling cascade stimulates cell proliferation, which may be responsible of the sustained growth of malformations in the three mentioned regions. The present study aims to explain the classic clinical manifestations of SSW from a genetic, molecular and pathophysiological perspective.

Key words: Sturge-Weber Syndrome; Genetics; Physiopathology (source: MeSH NLM).

RESUMEN

El síndrome de Sturge Weber (SSW) se caracteriza por el compromiso clásico de malformaciones vasculares neurooculocutáneas esporádicas, cuya fisiopatología hasta la fecha no se ha podido dilucidar del todo.

El descubrimiento de un perfil molecular tanto arterial como venoso en el endotelio presente en las malformaciones vasculares aunado a zonas de atresia vascular distales a las zonas ectásicas, han llevado a cuestionar las teorías embriológicas planteadas desde hace décadas, para explorar las características moleculares y genéticas en el tejido afectado.

A la actualidad se ha reportado una elevada prevalencia de la mutación somática en el gen GNAQ en los tejidos afectados de los pacientes con SSW el cual codifica una subunidad alfa de una proteína Gq, cuya cascada de señalización estimula la proliferación celular, pudiendo esta ser responsable del crecimiento sostenido de las malformaciones de las tres regiones mencionadas. El presente estudio se propone a explicar las manifestaciones clínicas clásicas del SSW desde un enfoque genético, molecular y fisiopatológico.

Palabras clave: Síndrome de Sturge-Weber; Genética; Fisiopatología (fuente: DeCS BIREME).

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INTRODUCTION

Sturge-Weber Syndrome, also known as encephalotrigeminal angiomatosis, within the phakomatoses group, together with neurofibromatosis, Klippel Trenaunay syndrome, Von Hippel-Lindau syndrome and tuberous sclerosis⁽¹⁻³⁾.

This possesses a classic compromise of sporadic neuro-ocular-cutaneous vascular malformations, with an estimated frequency of 1 per 50,000 live births without a defined hereditary pattern, without gender differences, nor malignant predisposition⁽¹⁻³⁾.

The diagnosis is established identifying 2 of the characteristics in its classic triad, port-wine stain (PWS), glaucoma and leptomeningeal malformations. In some situations, systemic manifestations may be present for other associated phakomatoses, which allows to classify SWS in 4 types^(2,4).

PHYSIOPATHOLOGY GENERALIZATIONS

Embryological theory

The classic theory explains the neuro-ocular-cutaneous anomalies in SSW due to the persistence of the primordial vascular plexus, an embryonic cephalic microvasculature present in the ectoderm, precursor of the integumentary facial tissue, eyeball and neuroectoderm destined for the genesis of the vascularization of the parieto-occipital cerebral area which, due to the alteration of the neural crest cells, does not regress during the estimated gestational age, which is week five to eight. Currently, the theory has been reinforced proposing somatic mutations that avoid said regression^(1,2,5-7).

Genetics and molecular bases

Chromosomal abnormalities have been reported, such as paracentric inversion of chromosome 4p and trisomy of chromosome 3 in cultures of fibroblasts from the affected regions due to leptomeningeal malformations in individuals with SSW⁽⁵⁾, at the same time the genes from region 17p1-p13 have been associated, related to retinitis pigmentosa, Klippel Trenaunay syndrome, phakomatosis pigmentovascularis, cerebral astrocytoma and subglottic stenosis⁽²⁾.

In 2013, Shirley et al found that in 92% of SSW, 88% of PWS and 0% of healthy dermal tissue, the somatic mosaic mutation of substitution of nucleotide Arg183Gln, in the GNAQ gene, located in chromosome 9q21, which codifies the alpha subunit of the Gq protein, which forms part of the

mitogen-activated protein kinase pathway (MAPK) together with protein kinases, ERK, JNK and stress-activated protein kinase (p38/SAPK), which control a series of processes such as cellular proliferation, cellular differentiation, apoptosis and cellular stress response, through the modest and non-multifaceted activation that could stimulate a sustained growth of vascular malformation, this way SSW was associated to MAPK pathway activation, a cellular growth and proliferation pathway. In comparison is the Gln209Leu mutation in the GNAQ gene, which leads to an excessive and multifaceted activation in the primary melanoma of the uvea and blue nevus^(2,8-10).

We found elevated levels of the vasoendothelial growth factor-A (VEGF-A) and an increase in the expression of its surface receptor in PWS and leptomeningeal malformations, which would generate an activation of the MAPK pathway⁽¹⁰⁾.

PORT-WINE STAIN

Definition and epidemiology

Port-wine stain has an incidence of 0.3-0.5% and is the most frequent vascular malformation in the neonatal stage, of multifactorial origin and located in the facial dermis, preferably in the hemiface, with an infrequent bilateral involvement, able to involve oral, gingival, lingual and/or pharyngeal mucosa. While recent studies propose that PWS follows the facial embryonic vascular distribution, the classic proposal mentions the involvement of sensory regions of the ophthalmic, maxillary and mandibular branches of the fifth cranial nerve, with a risk of 8% for SSW, becoming the reason for patient referral by the ophthalmology and neurology specialties to rule out complications. Among other important statistics for PWS, there is 78% for neuro-ocular disorders, mostly ipsilateral, when there is region V1 involvement and 26% when there is partial V1 involvement, 35% leptomeningeal vascular malformation in case of bilateral involvement of the V1 area. If there is palpebral involvement, there is 50% chance of presenting anomalies of the conjunctival, scleral, retinal and/or choroidal circulation, which is anterior and posterior pole of the eyeball, leading to glaucoma and/or choroidal vascular malformations, with an infrequent association between bilateral PWS and bilateral choroidal hemangioma, as well as high risk for leptomeningeal pathologies, although its absence does not exclude its presence^(1,2,5,6,8,10-15).

Physiopathology and clinic

The progressive dilation of capillaries and postcapillary



venules lead to vascular stasis generating a purplish tone due to an increase in deoxygenated hemoglobin, upon physical examination a positive vitreous-pressure is visualized, which is a disappearance of the red tone when applying pressure. It has been proposed that the decrease in the innervation of the affected vessels as a proposed theory to explain this finding. Unlike the vascular tumors, this does not present vascular proliferation and, to date, there has been no malignant growth reported, these are also different from infantile hemangiomas, which involute with time^(1,2,5,6,10,11,14).

Without treatment, the dermis of the compromised area may present a progressive thickening and evolve from stains to hypertrophic lesions, which are presented in a mean of 9 years and a standard deviation of 1-29 years, and finally nodular which are susceptible to pyogenic granulomas, eczematous dermatitis and spontaneous bleeding, occurring in two-thirds of 50 year old patients with a mean of 22 years with a standard deviation of 14-53 years^(3,6,10,11,14).

Molecular biology and histology

The genesis of the dermal arterioles and venules derive from the primary capillary plexus (PCP), the inhibition of EfhB2 and the expression of EpnB1, crucial for the dermic differentiation of PCP to arterioles, in case there is no EphB1 inhibition, by default PCP will differentiate in venules with the consistent expression of EphB1, the endothelium of anomalous vessels co-express endothelial progenitor cellular markers CD133 and CD166 and venous marker EphB1 and arterial marker EfhB2, generating a blood vessel with a venous and arterial cellular profile of hypermetabolic behavior, for which various studies suggest categorizing these vessels as venous-like vasculature, associated to an increase in vesicular exocytosis, possibly being responsible for paracrine signals to other endothelial cells, pericytes and fibroblasts and autocrine to its own cell. These molecular changes explain the predominant vascular phenotype in pericyte proliferation and basal membrane duplication without significant ectasia, prior to vascular dilation, which suggests that vascular dilation is a secondary abnormality, which are associated to the activation of the MAPK pathway by EphB1 and EfhB2⁽¹⁰⁾.

Fibroblasts display a hypermetabolic and hyperbiosynthetic state with abundant rough endoplasmic reticulum, Golgi apparatus, mitochondria and free ribosomes in its cytoplasm, possibly responsible for the evolution of PWS from stains to hypertrophic and nodular lesions, given by

the synthesis, exaggerated and disorganized deposits in its extracellular matrix, which could be the result of paracrine signals given by the endothelial cells of the anomalous cells to the fibroblasts⁽¹⁰⁾.

When analyzing the kinase profile in the MPAK pathway present in the PWS and each one of the evolving states of PWS, the activation of C-JUN and ERK kinases was found in the dermal biopsies of PWS, which explains the progressive development of this vascular malformation. Likewise, we found the activation of AKT kinase and phosphatidylinositol-3 kinase in hypertrophic PWS, and activation of the gamma subunit of phospholipase C in the majority of PWS of nodular presentation^(10,16).

OCULAR VASCULAR MALFORMATIONS

Definition and epidemiology

These venous malformations are characterized by decrease of flow, increase of venous pressure and vascular dilations, in the anterior pole as well as posterior pole of the eyeball. The most frequent ocular manifestation is glaucoma, which occurs in the anterior pole, present in 30-70% of cases, which once diagnosed requires annual routine evaluations since it is a chronic disease that progresses to vision loss^(1,2,5).

Glaucoma

Present in 72% when PWS compromises both lids and 21% when it compromises the upper lid, its most frequent form is open angle. It possesses a bimodal presentation, 60% is developed in infancy, these present increased corneal diameters (25%), myopia, megalocornea, buphthalmos, heterochromia iridis, associated to anterior chamber angle anomalies, with an increase in the resistance for aqueous humor outflow, and late presentation, 40% in childhood or early adulthood with a normal angle but an increase in episcleral venous pressure, caused by arteriovenous short circuits by episcleral hemangiomas^(1,2,5).

Among the applied mechanisms in the development of glaucoma in SSW, the following have been proposed: congenital malformations of the anterior chamber angle that leads to an increase in resistance of the aqueous humor outflow, compromising the Schlemm's canal drainage, an increase in episcleral venous pressure given by arteriovenous short circuits which could increase venous pressure and decrease the aqueous humor filtration, hypersecretion of fluids by the ciliary bodies that lead to an increase in the aqueous humor volume and premature aging of the Schlemm's canal trabecular meshwork⁽²⁾.



Choroidal hemangioma

Decrease in venous fluid decreases the vorticoso vein drainage, cause choroidal capillary dilation and expansion which leads to vascular ectasia, pressure elevation and susceptibility for rupture^(1,2,5,17).

Choroidal hemangiomas are present in 20-70% of cases, these are divided into diffuse (more frequent) and localized. Among its complications is the decrease in visual acuity generated by the exudative retinal detachment and macular edema. Among other complications are photoreceptor degeneration and optic disc coloboma. The association between bilateral PWS and bilateral choroidal hemangioma are infrequent⁽¹⁸⁾, currently only one case has been reported by Chavala et al.⁽¹⁹⁾ evidenced by ocular fundus, where these will be evidenced as dark red color. The ultrasound allows us to diagnose and monitor the choroidal hemangiomas, evaluate its extension, characteristics and echogenicity, especially when the patient presents media opacity⁽²⁾. Spectral domain optical coherence tomography is the gold standard for the evaluation of choroidal and retinal morphology, since it allows us to quantify the choroidal vascular thickness, morphology and caliber⁽²⁾.

ENCEPHALIC VASCULAR MALFORMATIONS

Definition and epidemiology

The classical cerebral malformations consist of cortical hypoplastic vessels and leptomenigeal malformations located preferably in parietal and occipital lobes, where 85% of patients have a unilateral involvement, with the bilateral presentation as a predictive indicator of poor prognosis, 75-90% of patients will present convulsions, 75% in a year and 90% within 2 years, for which it is suggested to initiate imaging studies to rule out leptomenigeal malformations between 4-6 months and a follow-up at 2 years of age, if the diagnosis has not yet been established, 50-75% present mental retardation, 20-60% hemiparesis and hemiatrophy contralateral to the compromised hemisphere, 40-60% present vascular headache, 40-45% present hemianopsia^(5,6,8,9).

Physiopathology and clinic

Classical cerebral malformations consist of cortical hypoplastic vessels and leptomenigeal malformations preferably located in the parietal and occipital lobes explained by the primordial vascular plexus persistence theory, corroborated with perfusion imaging findings giving macroscopic

evidence of dilated and tortuous venous vessels and absence of the central drainage of the communicating cortical venous system superficial to the dural venous system, which prevents a centrifugal venous flow, generating leptomenigeal cyanosis analogous to PWS resulting from venous stasis, venous pressure elevation and leptomenigeal thickening, which leads to a centripetal collateral venous drainage towards the deep medullary veins and subependymal cerebral veins. Among its complications are the genesis of a hypoxic environment in the drained cortical tissue, leading to neuronal injury and necrosis, probable managers of convulsions, progressive mental retardation and transitory neurological deficits, where later the repair by gliosis and dystrophic calcification deposits are macroscopically manifested in imaging studies as cerebral atrophy and cortical calcification foci. Independently, venous stasis would predispose a pro-thrombotic environment generating venous thrombosis, contributing to neuronal death and its consequences previously mentioned^(1,5,6,8,9,20).

Imaging studies allow us to observe the leptomenigeal malformations, cerebral atrophy, cerebral gliosis and cortical dystrophic calcification. Magnetic resonance with gadolinium contrast is the gold standard for leptomenigeal malformation diagnosis. T1 sequence allows us to visualize its extension, while T2 sequence allows us to observe associated lesions such as ipsilateral cortical atrophy in the leptomenigeal malformation region, ischemic and/or necrotic white substance areas seen as hyperintense, gliosis areas with a hypointense pattern, and ipsilateral lateral ventricle dilation. Perfusion magnetic resonance allows us to evidence cortical hypoperfusion beneath the malformation, explained by the alteration in the cortical venous drainage previously mentioned. Computerized tomography is the best imaging study for the observation of calcifications, and its main limitation is radiation exposure for the underage patient^(1,2,5,7).

The most frequent age with respect to the development of seizures fluctuates between 6-18 months, making it reasonable to initiate imaging studies between 4-6 months and its follow-up at 2 years of age, if a diagnosis has not yet been established. The most common type of seizure is focal motor with or without loss of consciousness, children that are most affected will have partial complex or generalized secondary seizures in the first or second year of life, which can be triggers for migraines and transitory neurological deficits. Mental retardation is most frequent in patients with early onset seizures (before 2



years of age), seizures refractory to medical treatment and bilateral leptomeningeal involvement^(2,5,6,8).

Molecular biology

Immunohistochemical studies have shown an increase in the VEGF presence in the vascular malformations, and an over-expression in its endothelium of VEGFR-1 and VEGFR-2 receptors, as well as an increase in the HIF-2alpha transcription factor, suggesting a continued state of hypoxia and vascular remodeling^(1,5,8).

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