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"STURGE-WEBER SYNDROME: A COMPREHENSIVE REVIEW OF CLINICAL FEATURES, DIAGNOSIS, AND MANAGEMENT"

Neurology

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ABSTRACT

Sturge Weber Syndrome is a rare congenital neurocutaneous syndrome characterised by facial capillary malformation and vascular abnormalities in the brain and eye, as it causes seizures, intellectual disabilities, headache and migraines, glaucoma, choroidal hemangiomas and stroke like symptoms. This review paper elaborates the genetic mutation of GNAQ gene, its normal function and its mutation in Sturge Weber Syndromek. This paper also discusses about the signs and symptoms, diagnosis and possible treatment strategies for this disease.

KEYWORDS

Encephalotrigeminal, leptomeninges, port wine stain, somatic mosaic mutation, GNAQ gene, hemiparesis, glaucoma, choroidal hemangioma, leptomeningeal angiomatosis.

INTRODUCTION

Sturge Weber Syndrome was first described in 1860 by a German physician and ophthalmologist, Rudolf Schirmer,in an infant with facial angioma and buphthalmos. In 1879, a British physician and neurologist, Willam Allen Sturge reported a case of a pediatric patient with infantile onset of unilateral seizures, bilateral facial angioma which was dark purple in appearance so named it as port wine stain and unilateral glaucoma. In late 1922, a British physician and dermatologist, Frederick Parks Weber noted radiological fractures which included calcifications of the affected cerebrum.

In 1935, a Swedish physician Hilding Bergstrand named the syndrome Sturge-Weber Syndrome. (1)

Is a sporadic congenital neurocutaneous syndrome also known as encephalotrigeminal angiomatosis which is generally characterized by angiomas which involves the face,choroid and leptomeninges. There is facial capillary vascular formation which is also known as the Port Wine stain or nevus flammeus, it affects skin in distribution of ophthalmic branch of trigeminal nerve. It manifests as atonic,tonic or myoclonic.(2)

ETIOPATHOGENESIS AND GENETICS

Sporadic developmental disorder caused by somatic mosaic mutation in the GNAQ gene located on the long arm of the chromosome no.9.(3)

The Cause

The GNAQ gene provides instructions for making guanine nucleotide-binding protein G(q) subunit alpha (Gαq). The Gαq is part of complex proteins that regulates signalling pathways to help control the development and function of blood vessels.

The mutation in the GNAQ gene results in Sturge Weber Syndrome which causes production of the protein with impaired function. Due to this, the altered Gαq protein cannot regulate the signaling pathways resulting in abnormally increased signaling. People with Sturge Weber Syndrome have aberrant and excessive vessel formation before birth as a result of the increased signaling disrupting the regulation of blood vessel development.

NORMAL GNAQ function

The GNAQ gene provides instructions for making guanine nucleotide-binding protein G(q) subunit alpha (Gαq).

The Gα protein is a part of trimeric G protein complex, this complex binds to other G protein coupled receptors. When the protein complex is bound to a receptor, the Gαq protein binds to the molecule of GTP and is activated. The activated Gαq protein then separates the protein complex and activates the signaling pathways which helps to regulate the development and function of blood vessels. The Gαq protein converts GTP to GDP, which inactivates the protein, which then reattaches itself to trimeric G protein complex, disabling the signaling pathways.(4)

IN Sturge Weber Syndrome

The GNAQ gene mutation associated with Sturge Weber Syndrome changes a single amino acid in the Gαq protein and replaces the amino acid arginine with glutamate at position 183 in the Gαq protein, this alternation is somatic mutation and is only present in certain cells in brain,eyes and skin that involved in blood vessel formation.

After the activation, the altered Gαq can't convert GTP to GDP due to which the protein is always active and in turn the signaling pathways are always ON, the increased signaling disrupts the regulation of blood vessel development and causes abnormal and excessive formation of vessels before birth.

EPIDEMIOLOGY

There has been an estimated prevalence of 1 in 20,000-50,000 live births with no known gender predisposition.

A study in Korean National Health Insurance evaluated the data with an incidence rate of Sturge Weber Syndrome approximately 3.08 per 100,000 per year.

In the United States a study from Minnesota showed an incidence of 0.19 per 100,000 per year.

A study in New York City evaluated the incidence of rare epilepsies showed an incidence of 1 in 40,900 for epilepsy related to Sturge Weber Syndrome, it is greater than prior estimates.

Although it is believed that Sturge Weber Syndrome does not affect a patient's life expectancy but the symptoms can severely impact the quality of life.(5)

The prognostic factors can be epilepsy, hemiparesis and mental delay which are the neurological signs.

The disease onset can be variable in accordance with the presence,onset,intractability of epilepsy,motor dysfunction and neurocognitive impairment.

SIGNS AND SYMPTOMS

Abnormal blood vessel growth (angiomas) in the skin, brain and eyes.

Skin Manifestations

Port wine birthmark- reddish purple birthmark usually on the face (forehead,eyelid,temple)- gets darker and thicker over time.

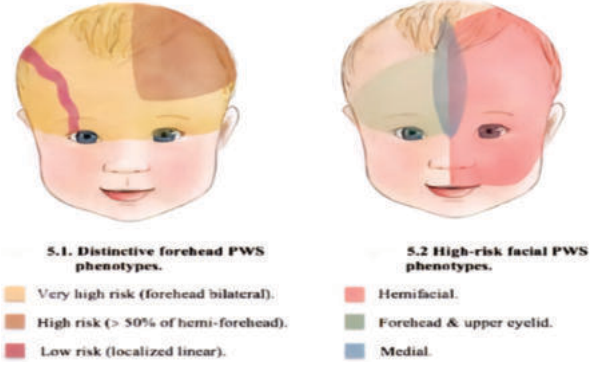

Fig-1(1)

Neurological manifestations
Seizures- starts by 1 year of age, usually occurs on only one side of the body, opposite to the birthmark but may also affect both sides of the body, could be

Focal-movements on one side of the body or altered awareness can range from brief moments of zoning out with repetitive motions to loss of consciousness.

Atonic- sudden loss of muscle tone which causes collapse.
Myoclonic- sudden brief twitches of arms and legs.
Infantile epileptic spasms-sudden brief muscle contractions which occur in clusters.

Hemiparesis and Hemiplegia- on opposite sides of the birthmark, it can worsen if seizures can't be controlled.(6)

Intellectual disability- more severe in patients- seizures start before 2 years of age and can't be controlled with medications, delay in motor and skill development, behavioural problems can occur.

Headache and Migraines- it is severe and can be treated with pain killers, it is often triggered with seizures and seizures can be triggered by headache.

Stroke Like Episodes- temporary weakness or neurological deficits which mimics a stroke- i.e hemiparesis or visual auras with migraine cause unilateral weakness which lasts longer than 24 hours seen in 6 months to 5 years of age.

Ocular Manifestations
Conjunctival episcleral and choroidal hemangiomas(tangles of abnormal blood vessels) in various parts of the eye, diffused one can lead to vision loss. They are generally present on the same side of the birthmark.

Glaucoma- can be present with two mechanisms-
1) Malformation of the anterior chamber
2) Elevated episcleral venous pressure (7)

In some patients the pressure may increase so much that the eyeballs appear bulged and enlarged (buphthalmos)

Other manifestations- growth and constitutional abnormalities, growth hormone deficiency,central hypothyroidism much higher than the general population.

DIAGNOSIS

Usually determined by Physical examination,Clinical typical symptoms,Facial appearance and Brain MRI.(8)

Ophthalmic Examination- to monitor Glaucoma every 2-3 or more under anesthesia in infants and young kids.

Ocular Ultrasound- for diffuse choroidal thickening which leads to choroidal hemangiomas.

Skull Radiograph- to see gyriform calcification gives the appearance of a "tram track" sign.

CT Scan- to detect calcifications, cortical atrophy and leptomeningeal enhancement. It uses ionizing radiation which is not recommended in children.

MRI of the Brain with contrast- it depends on the stage of the disease:
- In Early phase- there will be transient hyperperfusion,myelin maturation and leptomeningeal enhancement(i.e serpiginous enhancement)
- In Late phase- increased T2 signal in the region of gliosis with decreased pial enhancement,cortical atrophy,lack of superficial cortical veins and enlarged choroid plexus.

Electroencephalogram(EEG)- to check seizure activity.

Genetic testing of GNAQ gene- sequencing can confirm the Sturge Weber Syndrome, however clinical signs are enough to confirm the diagnosis.

Fluorodeoxyglucose-positron emission tomography (FDG-PET)- to study the cerebral metabolism, in the affected area:
- Early stages- Hypermetabolic
- Late stages- Hypometabolism (9)

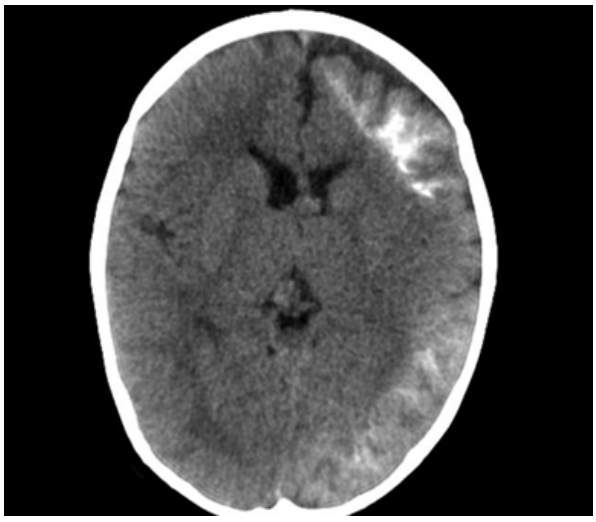

Fig.2(10)
The Left Hemisphere is atrophic and shows calcification.

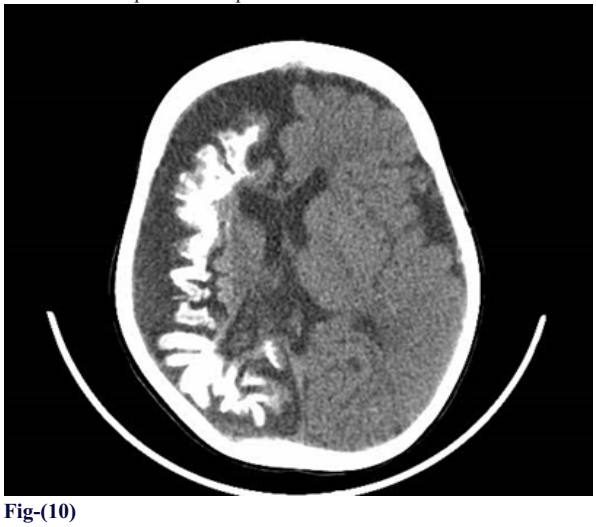

Fig-(10)
Unilateral right-sided atrophy of cerebral hemisphere with gyriform cortico-subcortical (tram-track) calcification is seen.

TREATMENT

There is no definitive cure, only symptomatic treatment is possible.

Port Wine- **Laser photocoagulation**- it does irreversible damage to blood vessels without damage to other skin compounds.

To minimize the seizure activity- **Antiepileptic medications** like Oxcarbazepin, Carbazepin, Phenytoin, Lamotrigine, Valproic acid
To decrease the frequency of seizures and stroke-like episodes- Low dose aspirin.(11)

Sx- Hemisphrectomy or focal resection of seizure focus, corpus callosotomy, vagal nerve stimulation.(12)

Glaucoma- the aim is to decrease the intraocular pressure, to reduce the risk of vision loss.

Topical medication is the 1st line for the late onset glaucoma-
Beta antagonist- eye drops- as it decreases the production of aqueous fluid.

Timolol, Betaxolol
Carbonic anhydrase inhibitor- decreases the production of aqueous fluid.

Dorzolamide, Brinzolamide

Adrenergic eye drops and mitotic eye drops- promote drainage of aqueous fluid.

Brimonidine,Apraclonidine.

Sx-Goniotomy or Trabeculotomy in patients with early onset glaucoma and association with angle abnormality. (13)

PROGNOSIS

The prognosis could be highly variable as it can range from mild to severe but it does not affect the lifespan but it affects the quality of life due to potential seizures,developmental delays and vision loss in glaucoma and cognitive issues. Early diagnosis and aggressive management are crucial for the better outcomes, however early seizure activity predicts the worse neurological outcomes.

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