

**Review Article**

**Spotlight on Sturge-Weber Syndrome:  
Unraveling the enigma of a rare  
neurocutaneous disorder in infants-An  
overview**

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**ABSTRACT**

This article aims to provide a concise overview of the existing literature on Sturge-Weber syndrome in infants. This comprehensive review presents key information regarding the prevalence, clinical characteristics, diagnostic methods, and available treatments based on recent global research. Sturge-Weber syndrome is a rare congenital neurocutaneous disorder, affecting approximately 1 in 20,000 to 50,000 new-born, and is caused by a somatic mutation in the GNAQ gene. Its defining features include leptomeningeal angiomas, glaucoma, and a facial birthmark known as a port-wine stain. Seizures are the most common neurological symptom, typically appearing within the first few months of life. Glaucoma can either manifest at birth or emerge during later stages of life. The severity of symptoms associated with Sturge-Weber syndrome can vary. Common treatments include anticonvulsants, laser therapy for the port-wine stain, and medication and surgery for glaucoma. This article also discusses potential causes, contributing factors, and possible solutions for Sturge-Weber syndrome.

*Keywords: Sturge-weber syndrome, facial port wine birth mark, Glaucoma, Leptomeningeal angioma*

**1. INTRODUCTION**

Sturge-Weber syndrome (SWS) is a rare spontaneous neurocutaneous disorder characterized by a facial birthmark caused by a capillary malformation in the ophthalmic distribution of the trigeminal nerve. It is associated with ipsilateral vascular glaucoma, vascular malformation of the eye, and a leptomeningeal angioma. A face angioma near the trigeminal nerve that is present at birth elevates the possibility of Sturge Weber Syndrome.<sup>[1]</sup> The facial port-wine birthmark (capillary malformation) is linked to abnormal blood vessels in the brain (leptomeningeal "angioma") and the eye, contributing to the development of SWS.<sup>[1,2]</sup> Glaucoma, resulting from vascular abnormalities in the eye, can lead to visual impairment. SWS is a genetic condition that presents a wide range of clinical symptoms, including isolated brain or eye involvement, as well as combined eye, skin, and brain involvement with birthmarks.<sup>[3]</sup>

The diagnosis of SWS typically requires the presence of a birthmark and eye involvement, although a subset of patients with both may be considered to have the syndrome. If a child has a facial birthmark and normal contrast-enhanced magnetic resonance imaging (MRI), the likelihood of developing brain involvement from SWS is low.<sup>[4,5]</sup>

SWS affects the venous microvasculature of the head, particularly the occipital and posterior parietal lobes, but it can also affect other cortical regions and both cerebral hemispheres. The asymmetrical facial vascular malformation usually affects the upper face, following the pattern of the trigeminal nerve's ophthalmic division<sup>[6]</sup> Seizures, glaucoma, headaches, transient stroke-like neurologic symptoms, and behavioral disorders are associated with SWS. Hemiplegia, hemiatrophy, and hemianopia may occur contralateral to the cortical abnormalities. If left untreated, there is an increased risk of hypothyroidism (often central) and growth hormone deficiency.<sup>[6,7]</sup>

## **2. LITERATURE REVIEW AND SEARCH STRATEGY**

Searches for pertinent papers in databases such as Science Direct, PubMed, the Cochrane Library, Embase, Medline, and generic Google search were conducted in-depth. Review on SWS, incidence and prevalence of Sturge weber syndrome in India and the rest of the world, and the complications and treatment algorithm of SWS were just a few of the search terms used. Although medical treatments have changed significantly in recent years, only pertinent publications that were appropriate for this review and articles published after 2000s & later were considered. The articles that covered comorbid conditions were excluded from this review. This review has been conducted without bias by taking into account research publications with both positive and negative findings.

## **3. INCIDENCE AND PREVALANCE**

Despite the absence of population-based studies, prevalence estimates range from 1 in 20 to 50,000 live births. In 1974, SWS was identified in a 2.5 months year old child, it was first recognized in India.<sup>[8,9]</sup>

## **4. HISTORICAL OVERVIEW**

William Allen Sturge initially gave a description of the syndrome in 1879. A 61-year-old female had a birthmark that extended from the right side's forehead up through the scalp, down across the breast, and up to the neckline. Sturge referred to this as a "mother's mark" and described it as a port-wine stain. The child has had "twitching on her left side of her body" since she was six months old.<sup>[10]</sup> Rudolf Schirmer (1831-1896) had earlier noted a 36-year-old man with a left facial nevus and buphthalmos. However, he made no mention of epilepsy or other brain disorders in his account.<sup>[11]</sup>

To further explain the pathophysiology of certain dermatological conditions, including SWS, Rudolf Happle put out the concept of somatic mosaic mutation in 1987. because there is no family inheritance pattern and the region of participation is asymmetric. A post-fertilization mutation in the developing fetus and a progenitor cell led to SWS. Since it described the fundamental method required to identify the suspected mutation, which involved comparing DNA from an affected area of the body with DNA from an unaffected area of the body, this notion was important to finally discover the underlying cause.<sup>[12]</sup>

Dermatologist William Allen Sturge (1850–1919), first identified a connection between facial birthmarks and seizures in 1879. F. Parkes Weber (1863-1962), the first to name the condition Sturge-Weber in 1922, conducted extensive study on brain calcification before others like Durk (1910), Volland (1912), Hebold (1913), and Krabbe (1932) did. By the 1940s, radiologists were routinely diagnosing SWS, with X-rays showing the typical tram track abnormalities. Dr. E. Steve Roach proposed classifying the "encephalotrigeminal angiomatosis" spectrum in 1992. It's important to remember that SWS is a spectrum condition in terms of the structures affected and the degree of their involvement, even though these labels haven't completely supplanted SWS as a diagnosis.<sup>[13]</sup>

## 5. CLASSIFICATION:

Sturge-Weber syndrome has been traditionally characterised based on the presence or absence of facial and leptomeningeal angiomas, according to Roach scale.<sup>[39]</sup>

<b>TYPE 1</b>	<i>Classic syndrome</i>
<ul style="list-style-type: none"><li>• with both facial and leptomeningeal angiomas; may have glaucoma</li></ul>	
<b>TYPE 2</b>	<i>Facial Angioma</i>
<ul style="list-style-type: none"><li>• without evidence of intracranial disease; may have glaucoma</li></ul>	
<b>TYPE 3</b>	<i>Isolated leptomeningeal angioma</i>
<ul style="list-style-type: none"><li>• No glaucoma</li></ul>	

**Fig 1. Classification of Sturge weber syndrome**

## 6. PATHOGENESIS

The water autohydrolysis region within the GTP-GDP binding site is affected by the Arg.183Gln mutation in GNAQ. The mutation is believed to reduce the efficiency of autohydrolysis, which reverts the guanine nucleotide protein to its inactive (GDP-bound) state and complex with its GPCR. This mutation will therefore probably permanently over activate downstream pathways. The R183Q mutant increased phosphorylated Extracellular signal-regulated kinase somewhat but statistically significantly more than the wild-type construct when transfected into a human kidney epithelial cell line (293T cells).<sup>[15]</sup> The Gq-alfa family of G proteins, which its gene product is a member of, serve as translators and modulators in numerous transmembrane signalling networks. Somatic mutations in GNAQ have been discovered in congenital hemangiomas (RICH and NICH), melanocytic neoplasms, uveal melanoma, and phacomatosis pigmentovascularis in addition to capillary abnormalities. Phacomatosis pigmentovascularis has been linked to mutations in the genes GNAQ and GNA11; in the instances examined, the same mutation was present in both the pigmentary and vascular components. These mutations promote proliferation and inhibit apoptosis by increasing signalling through Ras effector pathways.<sup>[16]</sup>

The GNAQ gene is located on chromosome 9 and consists of seven exons that total 310 993 nucleotides. The GNAQ gene is located on chromosome 9 and consists of seven exons that total 310 993 nucleotides. The Gq-alfa family of G proteins, which function as modulators and translators in a number of transmembrane signalling networks, includes the gene product of this protein. Along with capillary abnormalities, somatic mutations in GNAQ have been linked to melanocytic neoplasms, uveal melanoma, congenital hemangiomas (RICH and NICH), and phacomatosis pigmentovascularis. Phacomatosis pigmentovascularis has been associated with GNAQ and GNA11 mutations, and in the cases under investigation, the same mutation was discovered in both the pigmentary and vascular components.<sup>[15,16]</sup> These mutations boost signalling through the RAS effector pathways seen in Fig. 1 to promote proliferation and prevent apoptosis.

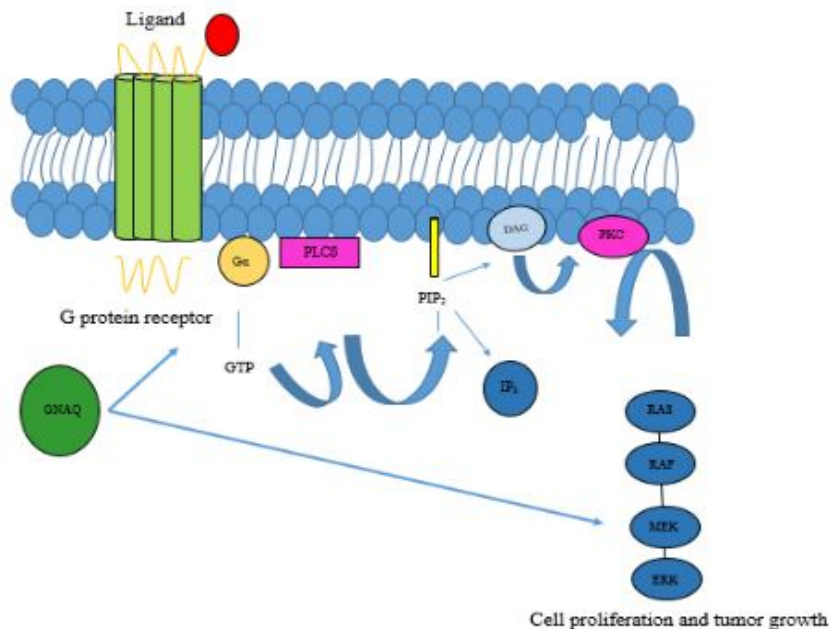


Fig2. Illustration of pathogenesis of sturge weber syndrome<sup>[36]</sup>

## 7. PATHOPHYSIOLOGY

The primitive cephalous venous plexus of SWS most likely failed to retract and grow normally during the first trimester, which led to the angioma that was found there. The embryological vascular anomalies have an impact on the nearby skin, ocular, and brain regions. The proximity of the ectoderm, which will eventually form the upper portion of the facial skin, to the neural tube, which will eventually form the parietal occipital areas of the brain at this stage of development, may help to explain the involvement of the trigeminal area of the skin and the parietal occipital leptomeningeal angioma.<sup>[17]</sup> A somatic mutation affecting the tissues' embryological progenitor has been suggested as a potential cause. This genetic theory is supported by three observations:

- (1) the identification of elevated fibronectin gene expression, pointing to a potential mutation in this gene;
- (2) some chromosomal abnormalities, such as paracentric inversion or chromosome 10 trisomy, in fibroblasts from affected skin areas; and
- (3) the occurrence of a few familial cases with a potential linkage to a region on 5q11– 23 that contains intriguing candidate genes involved in vasculogenesis and neurogenesis.<sup>[1, 17, 48]</sup>

## 8. CLINICAL CHARACTERISTICS

### 8.1 Port-wine birthmark:

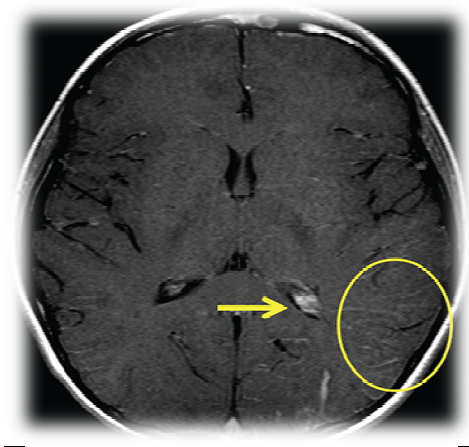
The majority of people with SWS have a port-wine birthmark. This type of blemish is brought on by the enlargement (dilation) of tiny blood vessels (capillaries) close to the skin's surface. Port-wine birthmarks can initially range in color from light pink to deep purple.<sup>[49]</sup>



**Fig 3. Portwine stain exhibiting as pink color upon a side of face**

### **8.2 Leptomeningeal angioma:**

Within the two thin layers of tissue that cover the brain and spinal cord, SWS is characterized by aberrant creation and proliferation of blood vessels. This anomaly, known as a leptomeningeal angioma, can affect one or both sides of the brain, obstructing blood flow and causing atrophy and calcium deposits (calcification) in the brain below the angioma. In persons with SWS, a reduction in blood flow produced by leptomeningeal angiomas can lead to stroke-like symptoms.<sup>[50]</sup>

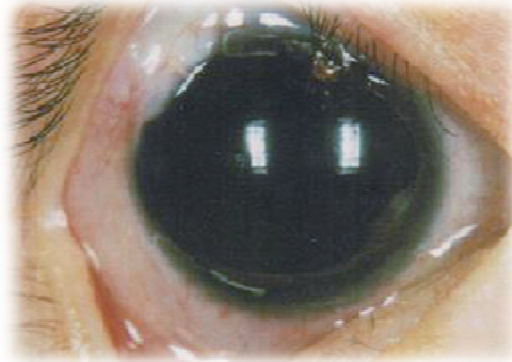


**Fig 4. Xray image showing Leptomeningeal angioma on brain, enlarged and enhancing left glomus angioma (arrow) and prominent trans medullary veins(circle)**<sup>[37]</sup>

### **8.3 Ocular Manifestation(Glaucoma):**

Glaucoma usually occurs in infancy or early adulthood in people with SWS, and it can cause vision loss. The pressure in some affected infants can become so high that the eyeballs appear swollen and bulging (buphthalmos). Hemangiomas (tangles of abnormal blood vessels) can form in various areas of the eye in people with SWS. A diffuse choroidal

hemangioma arises in around one-third of people with SWS when abnormal blood vessels grow in the network of blood vessels at the back of the eye (choroid).<sup>[14,18,19,20,51]</sup>



**Fig 5. Glaucoma in infancy<sup>[38]</sup>**

#### **8.4 Endocrine Manifestation:**

Hypothalamic-pituitary dysfunction, growth hormone insufficiency, and central hypothyroidism are all possible symptoms of SWS<sup>[18,19,20]</sup>

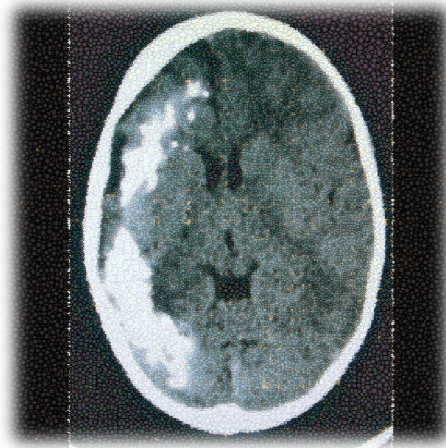
### **9. DIAGNOSIS**

In addition to a neurologic history, exam, and EEG, contrast enhanced MRI with postcontrast FLAIR and SWI, MRA, and MRV can be considered. Despite the fact that early infancy has minimal sensitivity. Cause Somatic mosaic mutation in GNAQ causes pathways downstream of the coding protein Gαq to become overactive. Neuroimaging can be obtained when symptoms first appear or after one year of age.

Sturge-Weber syndrome brain involvement is diagnosed via neuroimaging using contrast-enhanced magnetic resonance imaging (MRI); without contrast, the abnormal blood vessels will not be apparent. Susceptibility-weighted imaging and postcontrast flair are two MRI sequences that can increase sensitivity for diagnosis and the degree of brain involvement. Because contrast-enhanced MRI in infants and children has lower sensitivity. If neuroimaging is negative, it must be done again in new borns and young babies after the first year of life. The extent of brain involvement may also become more visible after the first year, therefore it's crucial to repeat the MRI at that point.

#### **9.1 Computed tomography:**

Children who develop hemiparesis or seizures are frequently assessed in the emergency room using a technique called brain tomography. As early as one year of age, computed tomography can identify calcifications, such as prominence of subependymal and medullary veins, volume loss in the affected brain hemisphere, and fast myelination beneath the leptomeningeal angioma. These alterations become more obvious after a year.



**Fig 6. CT shows gyri form calcifications with atrophy of right hemisphere<sup>[40]</sup>**

### **9.2 Electroencephalogram:**

Asymmetric electroencephalograms (EEG) in SWS patients show lower voltages and concentrated discharges in the brain's affected hemisphere. EEG can also assist in separating acute paroxysmal episodes caused by cerebrovascular events from headaches and seizures.

The EEG in SWS patients appears to change with time, growing steadily abnormal and displaying increasing epileptiform activity.<sup>[21,22]</sup>

### **9.3 Head X-Ray:**

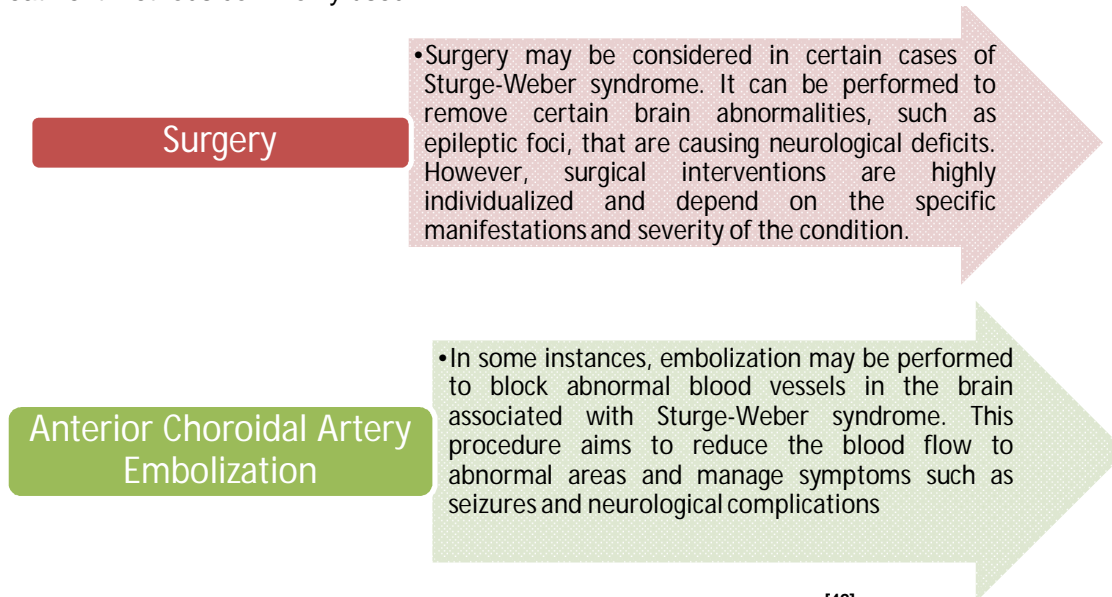
It is possible to view the characteristic gyri form cortical calcifications, also known as railway track appearance, which damage the intima layer of the meningeal arteries, even if simple X-ray is not the ideal method. These are located largely in the parietal and occipital areas, and they surround the leptomenigeal angioma. Calcifications are a late-onset finding in children since they frequently arise in those beyond the age of two.<sup>[23]</sup>



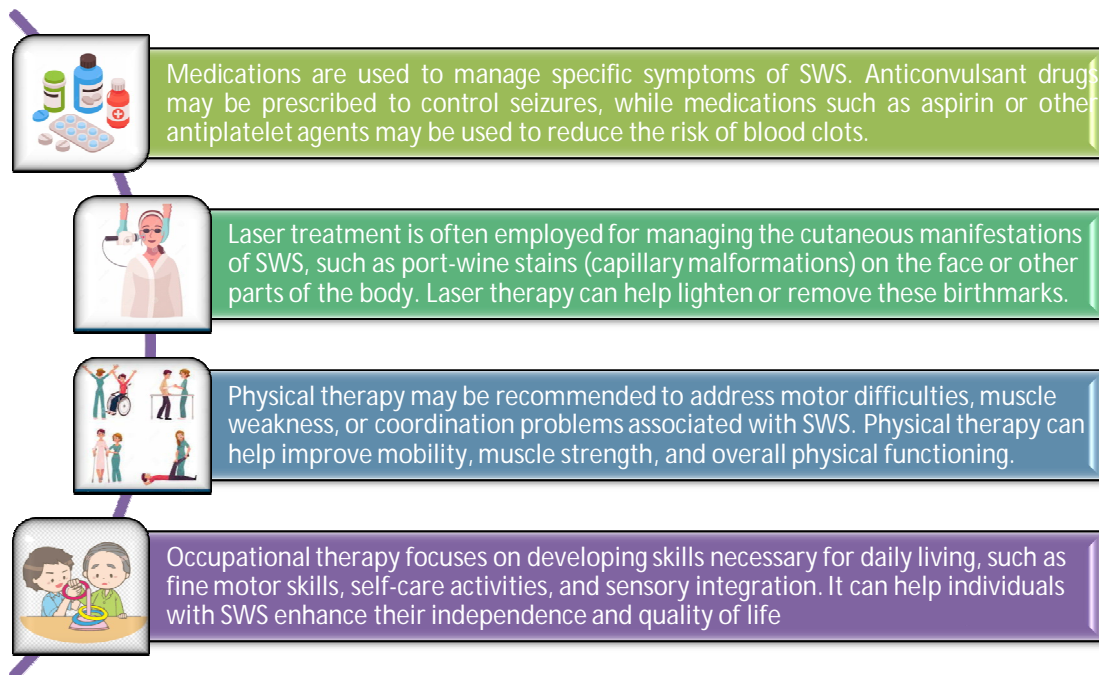
**Fig 7.X Ray of SWS patient shows tram line calcification<sup>[41]</sup>**

## 10. TREATMENT

The treatment approach for Sturge-Weber syndrome aims to manage symptoms and complications associated with the condition. Here are some invasive and non-invasive treatment methods commonly used



**Fig 8. Invasive Treatment Methods used in SWS<sup>[42]</sup>**



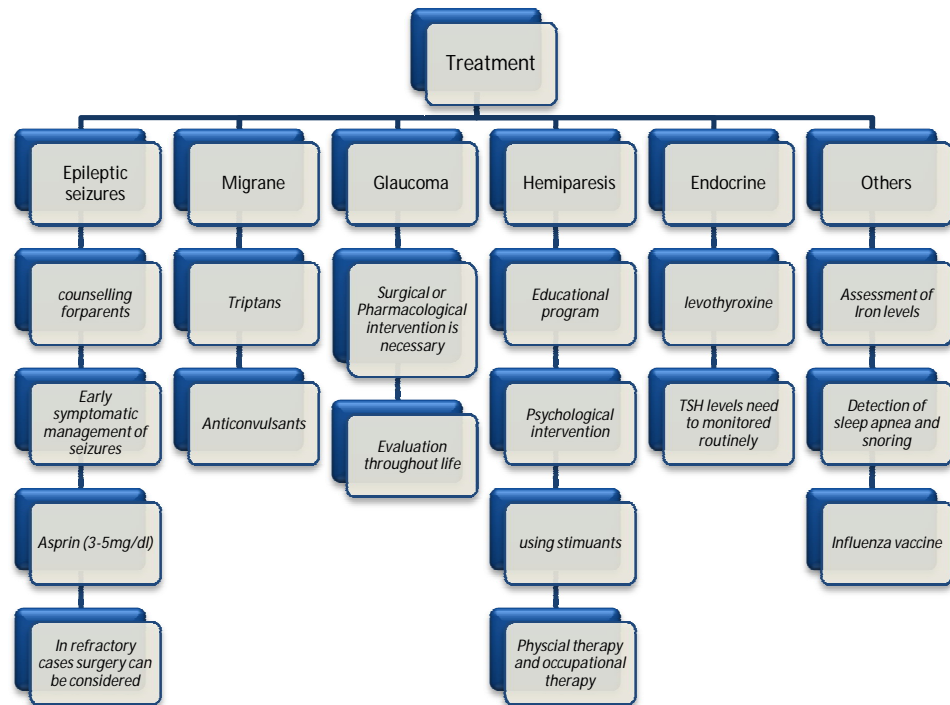
**Fig 9. Noninvasive treatment used in SWS<sup>[43]</sup>**

Effective PWS therapy uses laser technology. Some of the treatments that have been suggested include photocoagulation, photodynamic therapy, external beam radiation, brachytherapy, and anti-vascular endothelial growth factor. PDT is the most often used therapy to treat choroidal hemangiomas because it reduces leakage and produces vascular atrophy. PDT has only been applied to a small number of diffuse choroidal hemangioma instances, most likely because to the risk of foveal scarring and pigmentary changes. A different form of treatment for diffuse choroidal hemangioma made worse by serous retinal detachment is external beam radiation. Cobalt-60 and ruthenium-106 brachytherapy has been used to successfully treat exudative retinal detachment brought on by choroidal hemangiomas.<sup>[25,26]</sup>

The PWB is initially treated with laser procedures during infancy, when the flat, pink birthmark responds best and the birthmark is smaller. It takes a number of laser treatments before the birthmark is completely gone. Over time, the PWB recurs often, requiring continuing therapy. The cornerstone of neurologic treatment is anticonvulsants.<sup>[25]</sup>

Sturge-Weber syndrome epilepsy can be challenging to control since it frequently manifests as status epilepticus episodes and clusters of seizures. The most often prescribed anticonvulsants in infants are oxycarbazepine, leviteracitam, and phenobarbital. Infantile spasms can be treated with steroids, topiramate, vigabatrin, or a ketogenic diet in the small percentage of patients who develop them. Patients taking anticonvulsants like carbamazepine, lamotrigine, or oxcarbazepine develop a generalised spike and wave pattern on their electroencephalogram (EEG) that is linked to myoclonic seizures. These patients are frequently switched to anticonvulsants like valproate, leviteracitam, or topiramate, which treat both focal and generalised seizures. One or two anticonvulsants and low-dose aspirin can often control seizures in most people.<sup>[27]</sup>

Long-lasting seizures, especially in infants and young children, might cause stroke, hence antiepileptic medication should be used aggressively. Low-dose aspirin (3-5 mg/kg/day) is another therapy option, albeit not all groups use it. Infants with significant bilateral brain involvement may benefit from presymptomatic anticonvulsant and low-dose aspirin treatment because they are at the highest risk.<sup>[28,29]</sup> The hemispherectomy or hemispherotomy procedure, targeted resection, the ketogenic or Atkins diet, and the vagal nerve stimulator are further treatment options for patients whose seizures are unresponsive to anticonvulsant drugs. For patients with unilaterally afflicted who have failed two or more anticonvulsants as well as low-dose aspirin, surgery should be considered.<sup>[29]</sup> Even if seizures and other neurologic issues are not severe, surgery should be seriously considered in those whose cognitive development is progressively falling behind normal. Their cortex is vulnerable to ischemic brain damage, atrophy, and calcification. Anticonvulsants and low-dose aspirin should be the best therapy for these babies. Hemispherectomy, which is considered palliative rather than possibly curative, has been offered for children with very severe, disabling seizures that mostly originate from one hemisphere and who are bilaterally affected.<sup>[28,29]</sup> Ischemic brain damage, atrophy, and calcification are all threats for the cortex.<sup>[30]</sup> Anticonvulsants and low-dose aspirin should be used to treat these newborns aggressively.<sup>[29]</sup> Children with very severe disabling seizures that mostly originate from one hemisphere who are bilaterally affected have been suggested for hemispherectomy, which is considered palliative rather than potentially curative.<sup>[31,32,46,47]</sup>



**Fig10. Treatment Approaches of SWS**

## 11. COMPLICATIONS

### 11.1 Neurological complications:

Epilepsy, migraine, attention-deficit hyperactivity disorder, stroke and mental retardation like episodes. Seventy five to ninety five percent of children with Sturge weber syndrome have epilepsy<sup>[33,44]</sup>

### 11.2 Ocular complications:

The most predominant ocular complication associated with SWS is Glaucoma occurring in Thirty to seventy percent of patients.<sup>[33,44]</sup>

## 12. DISCUSSION

Sturge-Weber syndrome is brought on by a change in the GNAQ gene. This kind of gene mutation happens at random in the developing embryo and affects specific bodily tissues<sup>[34]</sup>. For this, in addition to a neurologic history, physical, and EEG, take into account contrast-enhanced MRI with postcontrast FLAIR and SWI, MRA, and MRV. EEG can be used to diagnose seizures in infants. SWS is an incurable, lifelong disease. Treatment of signs, however, can aid in averting complications. The use of laser therapy for PWS is efficient. Infantile spasms can be treated with steroids, topiramate, vigabatrin, or a ketogenic diet in the small percentage of patients who acquire them.<sup>[34,35,45]</sup> Referrals for children with high-risk

facial port-wine birthmarks (PWB) are advised, as are initial evaluation and continuing monitoring by paediatric neurologists and paediatric ophthalmologists. In newborns and infants with a high-risk PWB who have no history of seizures or neurological symptoms, routine brain imaging is not recommended, but it is possible in some cases. Routine follow-up neuroimaging is not recommended in kids with SWS and stable neurocognitive symptoms. Different ophthalmologic issues, such as glaucoma, necessitate different therapies depending on the patient's age and clinical presentation.<sup>[35,45]</sup> These recommendations might improve patient outcomes and help with care coordination for SWS patients.

### 13. CONCLUSION

In conclusion, Sturge-Weber syndrome (SWS) is a rare neurocutaneous disorder characterized by facial port-wine birthmarks, neurological abnormalities, and eye complications. This review article has provided an overview of the prevalence, clinical characteristics, diagnostic methods, and available treatments for SWS based on existing literature. The syndrome presents a wide spectrum of symptoms, including seizures, glaucoma, developmental delays, and intellectual disabilities. Early diagnosis and intervention are crucial in managing the condition and preventing potential complications. Further research is needed to explore novel therapeutic approaches. Increased awareness among healthcare professionals and improved access to specialized care can contribute to enhanced outcomes and quality of life for individuals with Sturge-Weber syndrome and their families

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## **ABBREVIATIONS:**

SWS: Sturge Weber Syndrome; GNAQ: Guanine nucleotide-binding protein; PWS: Port-Wine Stain; GTP-GDP: Guanosine Triphosphate -Guanosine Diphosphate; GPCR- G Protein Coupled Receptors; RICH-NICH: Rapidly Involuting Congenital Hemangioma- Non Involuting Congenital Hemangioma; RAS: Rat Sarcoma; DAG- 1,2 diacylglycerol; G- G protein; IP3- 1,4,5 triphosphates; PIP2- phosphatidylinositol 4,5- bisphosphate; PKC- protein kinase C; PLC- phospholipase C.FLAIR: Fluid-Attenuated Inversion Recovery; SWI: Susceptibility Weighted Imaging; MRI: Magnetic Resonance Imaging; MRV: Magnetic Resonance Venography; EEG: Electroencephalography; PDT: Photodynamic Therapy.