Review Article

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

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 angiomatosis, 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 whine 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.[1] 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 Sturge-Weber syndrome. [1,2] Glaucoma, resulting from vascular abnormalities in the eye, can lead to visual impairment. Sturge-Weber syndrome 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.[3]

The diagnosis of Sturge-Weber syndrome 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 Sturge-Weber syndrome is low. [4,5]

Sturge-Weber syndrome 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.[6] Seizures, glaucoma, headaches, transient stroke-like neurologic symptoms, and behavioral disorders are associated with SWS. Hemiplegia, hemi atrophy, 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. [6,7]

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 sturge weber syndrome 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, at the age of 2.5 months, Sturge Weber syndrome was first recognized in India. [8,9]

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. [10]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.[11]

To further explain the pathophysiology of certain dermatological conditions, including Sturge-Weber syndrome (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 Sturge-Weber syndrome. 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.[12]

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 Sturge-Weber syndrome (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 Sturge-Weber syndrome is a spectrum condition in terms of the structures affected and the degree of their involvement, even though these labels haven't completely supplanted Sturge-Weber syndrome as a diagnosis.[13]

5. TYPES OF SWS

There are three types of SWS.

5.1 Port-wine birthmark:

The majority of people with Sturge-Weber syndrome 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.

5.2 Leptomeningeal angioma:

Within the two thin layers of tissue that cover the brain and spinal cord, Sturge-Weber syndrome 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 Sturge-Weber syndrome, a reduction in blood flow produced by leptomeningeal angiomas can lead to stroke-like symptoms.

5.3 Ocular Manifestation(Glaucoma):

Glaucoma usually occurs in infancy or early adulthood in people with Sturge-Weber syndrome, 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 Sturge-Weber syndrome. A diffuse choroidal hemangioma arises in around one-third of people with Sturge-Weber syndrome when abnormal blood vessels grow in the network of blood vessels at the back of the eye (choroid). [14]

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). [15] 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.[16]

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.[15,16] These mutations boost signalling through the RAS effector pathways seen in Fig. 1 to promote proliferation and prevent apoptosis.

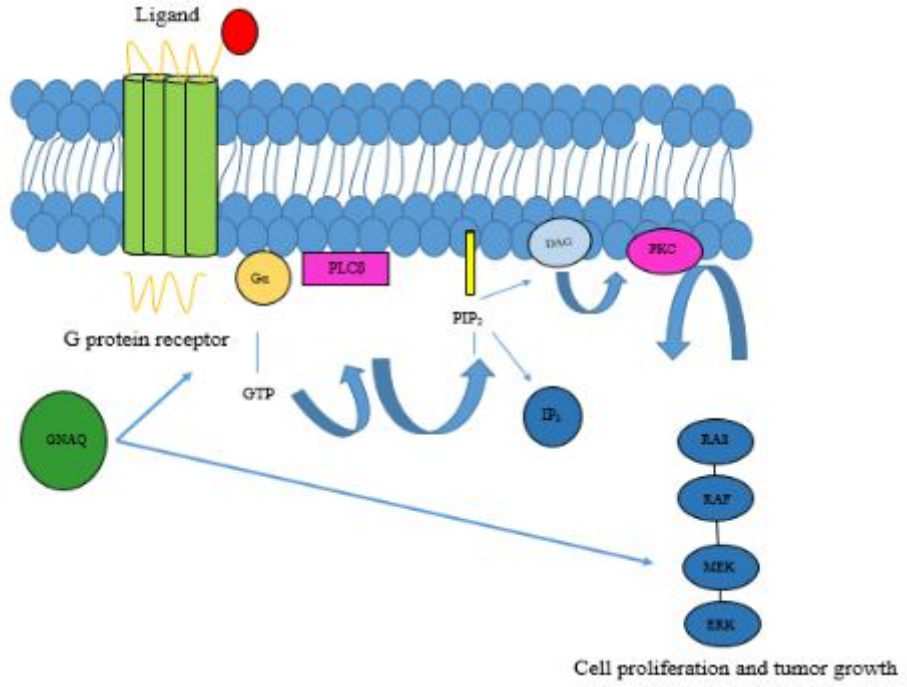

Fig 1. GNAQ is connected to cell development through the Mitogen-Activated Protein Kinase pathway, which cell membrane receptors use to transmit signals. This pathway's signalling is increased by an activating mutation, which could cause the capillary abnormalities seen in Sturge Weber syndrome..[36]

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.[17] 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.[1, 17]

8. CLINICAL CHARACTERISTICS

8.1 Skin Manifestation:

PWS, also known as capillary or venular malformation, is the most prevalent cutaneous sign of SWS. This birthmark fluctuates in colour from pale pink to purple, is variable in size, typically only affects one side, but can also affect both. PWS can be confused for simplex nevus (salmon spots). Capillary irregularities known as salmon patches manifest as rose-colored macules in the neck, philtrum, upper eyelids, forehead, and vertex.[18,19]

8.2 Neurological Manifestation:

Capillary-venous leptomeningeal malformation is one of the symptoms of SWS. PWS is frequently ipsilateral to intracranial angiomatosis, however it can sometimes be bilateral. It usually affects the occipital and occipitoparietal lobes, but it can also affect the entire hemisphere.[18]

8.3 Occular Effects:

Dilated tortuous venous veins in the conjunctiva, episclera, retina, and/or choroid cause optical atrophy and blindness. Glaucoma is one of the most common ocular symptoms of SWS, affecting 30% to 70% of patients. Retinopathy in SWS is thought to be caused by abnormalities in the anterior chamber that interfere with normal aqueous humour outflow, resulting in increased outlet resistance, or by increased episcleral venous pressure, a pathophysiological mechanism supported by the presence of blood within the Schlemm canal. Glaucoma may be present at birth or develop later. Dilated tortuous venous veins in the conjunctiva, episclera, retina, and/or choroid cause optical atrophy and blindness.
Choroidal hemangioma is found in 40 to 50 percent of SWS patients, and it can be confined or diffuse. The vascular choroidal lesion can sometimes take on a pathognomonic appearance, such as a reddish hue that has been compared to tomato ketchup colour. The choroid is typically unaffected during childhood, but it can thicken noticeably in teenagers and adults.[19,20]

8.4 Endocrine Manifestation:

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

9. DIAGNOSIS

In addition to a neurologic history, exam, and EEG, contrast enhanced MRI with postcontrast FLAIR and SWI, MRA, and MRV canbe considered. Despite the fact that early infancy has minimal sensitivity. Cause Somatic mosaic mutation in GNAQ causes pathways downstream of the coding protein Gaq 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.

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. [21,22]

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 leptomeningeal angioma. Calcifications are a late-onset finding in children since they frequently arise in those beyond the age of two. [23]

10. TREATMENT

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. [25,26]

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.[25]

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 spams 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.[27]

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. [28,29]. 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.[29] 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. [28,29] Ischemic brain damage, atrophy, and calcification are all threats for the cortex.[30] Anticonvulsants and low-dose aspirin should be used to treat these newborns aggressively.[29] 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.[31,32]

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.[33]

11.2 Ocular complications:

The most predominant ocular complication associated with SWS is Glaucoma occurring in Thirty to seventy percent of patients. [33]

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[34]. 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 spams can be treated with steroids, topiramate, vigabatrin, or a ketogenic diet in the

small percentage of patients who acquire then. [34,35]. 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 glaucoma, necessitate different therapies depending on the patient's age and clinical presentation. [35] These recommendations might improve patient outcomes and help with care coordination for SWS patients.

13. CONCLUSION

To achieve optimal care, a thorough analysis of the SWS etiology must be conducted in order to provide the best possible therapy. In addition, the best method for detecting and diagnosing presymptomatic brain involvement must be given top importance. A well developed treatment guidelines is necessary to manage this condition and to prevent complications. Each patient response to treatment has to be monitored thereby outcome can be improved & patient's quality of life can be enhanced.

REFERENCES

1. Comi AM. Sturge-Weber syndrome. Handb Clin Neurol. 2015;132:157-68.
2. Singh AK, Keenaghan M. Sturge-Weber Syndrome. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459163/
3. Mantelli F, Bruscolini A, La Cava M, Abdolrahimzadeh S, Lambiase A. Ocular manifestations of Sturge-Weber syndrome: pathogenesis, diagnosis, and management. Clin Ophthalmol. 2016 May 13;10:871-8.
4. Comi A. Current Therapeutic Options in Sturge-Weber Syndrome. Semin Pediatr Neurol. 2015 Dec;22(4):295-301.
5. Shirley MD, Tang H, Gallione CJ, Baugher JD, Frelin LP, Cohen B, North PE, Marchuk DA, Comi AM, Pevsner J. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ. N Engl J Med. 2013 May 23;368(21):1971-9.
6. Kentab AY. Klippel-Trenaunay and Sturge-Weber overlapping syndrome in a Saudi boy. Sudan J Paediatr. 2016;16(2):86-92.
7. Comi AM, Bellamkonda S, Ferenc LM, Cohen BA, Germain-Lee EL. Central hypothyroidism and Sturge-Weber syndrome. Pediatr Neurol. 2008 Jul;39(1):58-62.
8. Rihani HT, Dalvin LA, Hodge DO, Pulido JS. Incidence of Sturge-Weber syndrome and associated ocular involvement in Olmsted County, Minnesota, United States. Ophthalmic Genet. 2020 Apr;41(2):108-124.
9. Comi AM. Update on Sturge-Weber syndrome: diagnosis, treatment, quantitative measures, and controversies. Lymphat Res Biol. 2007;5(4):257-64.
10. Pearce JM. Sturge-Weber syndrome (encephalotrigeminal or leptomeningeal angiomatosis). J Neurol Neurosurg Psychiatry. 2006 Nov;77(11):1291-2
11. Schirmer R. Ein Fall von Telangiektasia. *Albrecht von Graefes Arch Ophtalmol* 18607119–121.
12. Happle R. Lethal genes surviving by mosaicism: a possible explanation for sporadic birth defects involving the skin. J Am Acad Dermatol. 1987 Apr;16(4):899-906.
13. Anne M. Comi, Douglas A. Marchuk, Jonathan Pevsner, Chapter 81 - Sturge–Weber Syndrome, Editor(s): Roger N. Rosenberg, Juan M. Pascual, Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease (Fifth Edition), Academic Press, 2015, Pg: 945-953

14. Jordan PR, Iqbal M, Prasad M, Sturge-Weber syndrome type 3 manifesting as 'Status migrainosus' *Case Reports* 2016;**2016:**bcr2016216842.
15. Comi AM. Presentation, diagnosis, pathophysiology, and treatment of the neurological features of Sturge-Weber syndrome. Neurologist. 2011 Jul;17(4):179-84.
16. Jansen P, Müller H, Lodde GC, et al. GNA14, GNA11, and GNAQ Mutations Are Frequent in Benign but Not Malignant Cutaneous Vascular Tumors. Front Genet 2021; 12:663272.
17. Comi AM. Topical Review: Pathophysiology of Sturge-Weber Syndrome. Journal of Child Neurology. 2003;18(8):509-516.
18. Palheta Neto FX, Vieira Junior MA, Ximenes LS, Jacob CCS, Rodrigues Junior AG, Palheta CP, et al. Clinical Features of Sturge-Weber Syndrome. Int. Arch. Otorhinolaryngol. 2008;12(4):565-570
19. Jagtap S, Srinivas G, Harsha KJ, Radhakrishnan N, Radhakrishnan A. Sturge-Weber syndrome: clinical spectrum, disease course, and outcome of 30 patients. J Child Neurol. 2013 Jun;28(6):725-31.
20. Helmi HA, Alkatan HM, Al-Essa RS, Aljudi TW, Maktabi AMY, Eberhart CG. Choroidal hemangioma in Sturge Weber syndrome: Case series with confirmed tissue diagnosis. Int J Surg Case Rep. 2021 Dec; 89:106626
21. Chugani HT, Mazziotta JC, Phelps ME. Sturge-Weber syndrome: a study of cerebral glucose utilization with positron emission tomography. J Pediatr. 1989 Feb;114(2):244-53.
22. Comi AM. Update on Sturge-Weber syndrome: diagnosis, treatment, quantitative measures, and controversies. Lymphat Res Biol. 2007;5(4):257-64.
23. Raval DM, Rathod VM, Patel AB, Sharma B, Lukhi PD. Sturge-Weber Syndrome: A Rare Case Report. Cureus. 2022 Sep 5;14(9).
24. Mantelli F, Bruscolini A, La Cava M, Abdolrahimzadeh S, Lambiase A. Ocular manifestations of Sturge-Weber syndrome: pathogenesis, diagnosis, and management. Clin Ophthalmol. 2016 May 13;10:871-8.
25. Hennedige AA, Quaba AA, Al-Nakib K. Sturge-Weber syndrome and dermatomal facial port-wine stains: incidence, association with glaucoma, and pulsed tunable dye laser treatment effectiveness. Plast Reconstr Surg. 2008 Apr;121(4):1173-1180.
26. Sebold AJ, Day AM, Ewen J, Adamek J, Byars A, Cohen B, Kossoff EH, Mizuno T, Ryan M, Sievers J, Smegal L, Suskauer SJ, Thomas C, Vinks A, Zabel TA, Hammill AM, Comi AM. Sirolimus Treatment in Sturge-Weber Syndrome. Pediatr Neurol. 2021 Feb;115:29-32
27. Kaplan EH, Kossoff EH, Bachur CD, Gholston M, Hahn J, Widlus M, Comi AM. Anticonvulsant Efficacy in Sturge-Weber Syndrome. Pediatr Neurol. 2016 May;58:31-6
28. Lance EI, Sreenivasan AK, Zabel TA, et al. Aspirin use in Sturge-Weber syndrome. Side effects and clinical outcomes. *J Child Neurol.* 2013;28:213–218.
29. Day AM, Hammill AM, Juhász C, Pinto AL, Roach ES, McCulloch CE, et al. Hypothesis: Presymptomatic treatment of Sturge-Weber Syndrome With Aspirin and Antiepileptic Drugs May Delay Seizure Onset. Pediatric Neurology. 2019; 90 :8–12.
30. Yeom S, Comi AM. Updates on Sturge-Weber Syndrome. Stroke. 2022 Dec;53(12):3769-3779.
31. Lew SM. Hemispherectomy in the treatment of seizures: a review. Transl Pediatr. 2014 Jul;3(3):208-17.
32. Arzimanoglou AA, Andermann F, Aicardi J, Sainte-Rose C, Beaulieu MA, Villemure JG, Olivier A, Rasmussen T. Sturge-Weber syndrome: indications and results of surgery in 20 patients. Neurology. 2000 Nov 28;55(10):1472-9.
33. Thomas-Sohl KA, Vaslow DF, Maria BL. Sturge-Weber syndrome: A review. Pediatric Neurology. 2004 May;30(5):303–10.
34. Dompmartin A, van der Vleuten CJM, Dekeuleneer V, Duprez T, Revencu N, Désir J, Te Loo DMWM, Flucke U, Eijkelenboom A, Schultze Kool L, Vikkula M, Boon L. GNA11-

mutated Sturge-Weber syndrome has distinct neurological and dermatological features. Eur J Neurol. 2022 Oct;29(10):3061-3070.
35. Sabeti S, Ball KL, Bhattacharya SK, Bitrian E, Blieden LS, Brandt JD, Burkhart C, Chugani HT, Falchek SJ, Jain BG, Juhasz C, Loeb JA, Luat A, Pinto A, Segal E, Salvin J, Kelly KM. Consensus Statement for the Management and Treatment of Sturge-Weber Syndrome: Neurology, Neuroimaging, and Ophthalmology Recommendations. Pediatr Neurol. 2021 Aug;121:59-66.
36. Higueros E, Roe E, Granell E, Baselga E. Síndrome de Sturge-Weber: revisión. Actas Dermosifiliogr. 2017;108:407---417.

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- phosphorylase C.FLAIR: Fluid-Attenuated Inversion Recovery; SWI: Susceptibility Weighed Imaging; MRI: Magnetic Resonance Imaging; MRV: Magnetic Resonance Venography; EEG: Electroencephalography; PDT: Photodynamic Therapy.