Systematic Review: Epilepsy in Sturge Weber Syndrome
Revisão Sistemática: Epilepsia na Síndrome de Sturge Weber

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ABSTRACT
Introduction: Sturge Weber syndrome (SWS) is a rare, non-hereditary, congenital developmental condition. Abnormal embryological development would be the cause of this disease. The intensity of this process and its extension to adjacent tissues are responsible for the variety of expressions of the syndrome. The main characteristics are the presence of a facial spot at birth, known as port wine, and alterations in the central nervous system, like seizures and mental retardation.

Objective: to evaluate the available surgical treatments for SWS epilepsy.

Methods: The PubMed and LILACS databases were used, using "treatment" as selection criteria. A total of 18 papers selected were organized in a table for statistical analysis.

Results: The majority of studies concluded that both clinical and surgical treatments could be effective in the management of SWS epilepsy, although its effectiveness depends on the disease progression.

Conclusion: Clinical and surgical methods should be considered in the treatment of SWS epilepsy. An unanswered question that still remains is whether suppression of seizures could prevent future neurological symptoms and cognitive decline.

Keywords: Sturge Weber syndrome; Treatment; Epilepsy

RESUMO
Introdução: A síndrome de Sturge Weber (SSW) é uma condição de desenvolvimento congênita rara e não hereditária. O desenvolvimento embriológico anormal é a causa desta doença. A intensidade desse processo e sua extensão aos tecidos adjacentes são responsáveis pela variedade de expressões da síndrome. Suas principais características são a presença de uma mancha facial ao nascer conhecida como vinho do porto e alterações no sistema nervoso central, como convulsões e retardamento mental. Objetivo: avaliar os tratamentos cirúrgicos disponíveis para a epilepsia SWS.

Métodos: Foram utilizadas as bases de dados PubMed e LILACS, utilizando “tratamento” como critério de seleção. O total de 18 artigos selecionados foi organizado em uma tabela para análise estatística.

Resultados: A maioria dos estudos concluiu que tanto o tratamento clínico quanto o cirúrgico podem ser eficazes no manejo da epilepsia SWS, embora sua eficácia dependa da progressão da doença.

Conclusão: Os métodos clínicos e cirúrgicos devem ser considerados no tratamento da epilepsia SWS. Uma questão sem resposta que ainda permanece é se a supressão das convulsões poderia prevenir futuros sintomas neurológicos e declínio cognitivo.

Palavras-chave: Síndrome de Sturge Weber; Tratamento; Epilepsia

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Sturge Weber syndrome (SWS), encephalotrigeminal angiomatosis or craniofacial angiomatosis is a rare, non-hereditary, and congenital developmental condition. The proportion of cases is 1/50,000 births.

The syndrome was initially described by Schirmer, in 1860, and Sturge described it further in 1878, mentioning its neurological manifestations. In 1992, Weber completed the description of the syndrome by documenting the brain radiological changes in these patients.

Abnormal embryological development would be the cause of this disease. In the sixth week of intrauterine life, the primitive cephalic venous plexus begins to be developed in the region of the ectoderm responsible for forming the facial skin. This vascular proliferation regresses in the ninth week. Failure to regress this primitive plexus results in a residual vascular tissue that will form angiomas in the leptomeninges, face and choroid. It is believed that the association between vascular malformations in the face and brain is due to the close proximity between the ectoderm and the cephalic portion of the neural tube. The intensity of this process and its extension to the adjacent tissues are responsible for the variety of expressions of the syndrome.

Angiomas involving the leptomeninges and the skin of the face, preferably in the path of the trigeminal nerve in the ophthalmic and maxillary branches, mark this disease. The main characteristics are the presence of a facial spot at birth known as port wine (Figure 1) and alterations in the central nervous system, like seizures and mental retardation.

The diagnosis is determined by the presence of neurological, cutaneous and ophthalmological alterations identified through cranial radiography and computed tomography.

The goal of this systematic review was to investigate the possible treatments for the main neurological manifestation in Sturge Weber syndrome: epilepsy.

We conducted a search in PubMed and LILACS databases from 1989 to 2019. The search strategy focused on the following keywords: ‘Sturge Weber’, ‘Epilepsy’, ‘Treatment’ and ‘Surgical Treatment’. Language was also a selection criteria, including only articles in Portuguese, Spanish, or English. Only articles providing data regarding to the treatment of neurological manifestations of patients harboring SWS were included (Figure 2).
Eighteen articles were included in this review, totaling 306 patients. The articles were written between 1989 and 2019. All data collected was summarized in a table, including the conclusion, treatment, year and number of patients evaluated. Among these patients, 242 patients tried clinical treatment and 186 had surgical treatment. First, they undertook clinical treatment, if it was not enough to contain the seizures, surgical treatment was necessary. In the surgical group, 77% underwent hemispherectomy.

Table 1. Epilepsy in Sturge Weber syndrome

| Author/Year | # Patients, Age | Clinical treatment | Surgical treatment | Results |
|-------------|-----------------|--------------------|--------------------|---------|
| Triana Junco PE, et al., 2019¹ | 1 male patient 36 weeks | Sirolimus, Aspirin | No surgical treatment (bilateral SWS) | Patient with extensive bilateral SWS in association with SWS has shown no seizure activity under medical treatment with aspirin and sirolimus. Significant improvement was observed since the first session of PDL treatment |
| Maraña Pérez AI, et al., 2017² | 13 patients (54% male and 46% female) Mean age at diagnosis: 15 months | Valproic Acid | Hemispherectomy | 31% of patients had to associate more than 3 drugs, 15% three drugs and 31% two drugs to obtain seizure control. Only 23% experienced good seizure control under monotherapy. Only one patient who underwent surgery (left hemispherectomy) for epilepsy remained seizure free without drugs |
| Nabbout R & Juhász C, 2013³ | 32 patients Mean age: 8 years | No use of antiepileptics | Hemispherectomy | A survey on the results of 32 worldwide hemispherectomies found that children undergoing hemispherectomy presented at a young age and had frequent seizures for approximately 1 year before surgery, after surgery 81% were seizure free |
| Jagtap S, et al., 2012⁴ | 30 patients (50% male and 50% female) Mean age: 11 years (1 month to 43y) | Anticonvulsant drugs (carbamazepine, followed by clobazam) | 10% Lobectomy (two occipital lesoiectomies and one occipital lobectomy) | 30% had simple partial seizures and 70% had complex partial seizures. Seizures were well controlled in 22 patients with antiepileptic drugs. Patients with refractory epilepsy required surgical treatment and after were seizure free |
| Lo W, et al., 2011⁵ | 27 children Mean age: 13 years (range 9-17 years) | Antiepiletics | 30% had hemispherectomies (three were functional and five were anatomic) | Patients who improved developmental functions had surgery at a mean age of 4 years and 5 months, while those who did not improve had surgery at mean age of 9 years and 8 months |
| Collettini F, et al., 2011⁶ | 1 patient 16 year old boy | Antiepiletics | Peri-insular hemispherectomy | The patient had complete seizure control and no permanent worsening of preoperative motor functions |
| Jiruska P, et al., 2011⁷ | 1 patient 2 years boy | Vigabatrin, Carbamazepine, Primidone, Valproic Acid, Phenytoin and Topiramate | Left occipital and temporal lobectomy | The medications resulted in a transient decrease in seizure frequency. After the surgery the patient was seizure-free for one year. One-year seizure-free periods were achieved after adjustments of treatment |
| Pascual-Castroviejo I, et al., 2008⁸ | 55 patients (30 males and 25 females) Mean age: 24 months | Carbamazepine, Levetiracetam | 3% Lobectomy | Surgical treatment can be successful with functional hemispherectomy in patients with bilateral SWS. The worst prognosis is observed in patients with bilateral lesions |
Table 1. Epilepsy in Sturge Weber syndrome (continued)

| Author/Year               | # Patients, Age          | Clinical treatment                  | Surgical treatment                                                                 | Results                                                                                                                                                      |
|---------------------------|-------------------------|-------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bourgeois M, et al., 2007 | 27 patients (52% male and 48% female) Median age at seizure onset: 9.1 months (range 1.9 months–12.3 years) | Antiepiletics                        | 29% Hemispherectomy, 14% Occipital, 14% Parietooccipital, 11% Parietal, 11% Temporoparietooccipital, 7% Temporal, 3% tempoporoparietooccipital, 3% Frontotemporoparietal | 16 patients had improved developmental functions after surgery, while 10 did not change and 1 worsened                                                                 |
| Schropp C, et al., 2006   | 8 patients Mean age: 15 months | Carbamazepine, Phenobarbital         | 87.5% Left Hemispherectomy, 12.5% Right Hemispherectomy affected                   | Five patients with unilateral angiomatosis were seizure-free without medication, rare non-disabling seizures occurred in one. Two patients had seizure reduction of > 90% |
| Comi AM, 2006             | 32 patients             | No use of antiepileptics             | Hemispherectomy                                                                    | The results of 32 hemispherectomies found that 81% were seizure free, motor function did not worsen                                                      |
| Di Rocco C & Tamburini G, 2006 | 14 patients Mean age: 11.5 years | Carbamazepine with Phenobarbital, Phenitoyn (second line) | 100% lobectomy                                                                     | Only one of them was seizure-free, although surgery was beneficial to all. All of those who underwent complete lesionectomy were seizure-free, whereas seizures persisted in the three patients who had partial resection of the angiomata |
| Baselga E, 2004           | 32 patients             | Carbamazepine, Sodium valproate, Phenobarbital | 100% hemispherectomies                                                            | 81% were seizure-free after surgery Cognitive deterioration may even improve after surgery                                                              |
| Tuxhorn IEB & Pannek HW, 2002 | 2 patients (2 female) Mean age: 1 year | Phenytoin, Phenobarbital, Valproate, Carbamazepine, Oxcarbazepine, and Vigabatrin | Hemispherectomy                                                                    | Successful surgical treatment with functional hemispherectomy was followed by good long term seizure control in both patients |
| Prayson RA, 2000          | 1 male patient 11 months | Antiepiletics                        | Functional Hemispherectomy                                                         | Surgery can potentially ameliorate epilepsy in patients less than 1 year of age. After the surgery, were seizure free                              |
| Arzimanoglou A & Alcardi J, 1992 | 23 patients Mean age: 10.5 years (range: 9 months-18 years) | Vigabatrin                           | 13% had localized cortical resection, 13% hemispherectomy and 8% lobectomy          | Complete control was obtained with one or two drugs in three patients. Partial control was obtained in five patients, most of whom received two or more drugs |
| Ito M, et al., 1990       | 6 patients (5 male and 1 female) Mean age 1 year (range 3 months and 4 years) | Antiepiletics                        | 50% Hemispherectomy                                                               | Hemispherectomy was effective for the control of medically intractable seizures in all three cases. The seizures disappeared postoperatively in all patients, and anticonvulsant administration was not needed |
| Bye AM, et al., 1989      | 1 patient (female) Mean age 4.5 years | Phenobarbitone, sodium valproate, carbamazepine, clobazam and intermittent clonazepam failed | Occipital Lobectomy                                                               | A neuropsychological assessment in the postoperative phase did not reveal significant changes compared with pre-operative performances |
Sturge-Weber syndrome has cutaneous, ocular and neurological manifestations

As cutaneous manifestation, facial angioma (or port wine stain) (Figure 1) is a capillary malformation that can grow proportionally with the child and usually does not regress spontaneously. They are almost always present in SSW and one of the first symptoms to appear. The characteristics of the facial angioma may define a higher risk factor for development of glaucoma and neurological manifestations.

The ocular manifestations include glaucoma and vascular malformations in the conjunctive, episclera, choroid and retina.

Neurological manifestations are caused by the presence of vascular malformations. The reduced blood supply in the affected hemisphere causes progressive destruction of the parenchyma and subsequent atrophy, epileptogenesis and neurological deficits.

The most frequent symptoms are seizures, mental retardation, headache, hemiplegia and hemianopsia. Seizures are the biggest risk factor for mental retardation and emotional and behavioral changes, so it is the symptom that seeks management or treatment.

The management of seizures in SWS is not an easy task. Anticonvulsants are the first-line therapy for patients with epilepsy related to SWS. In one report, adequate control was accomplished with anticonvulsant therapy in approximately 40% of the cases. In a retrospective single center report that analyzed a database of 108 subjects with SWS and one or more prior seizures, carbamazepine and oxcarbazepine were associated with better seizure control than levetiracetam, but no drug was clearly superior.

Carbamazepine and levetiracetam were commonly used alone or in combination, but subjects using oxcarbazepine or carbamazepine had better seizure control when compared with those subjects not using these medications and with subjects using levetiracetam. Oxcarbazepine was also associated with fewer side effects. Therefore, the investigators recommended starting with oxcarbazepine unless features of generalized seizure are present.

Although seizures of patients with SWS are reasonably controlled with one or two anti-seizure medications, in patients whose seizures fail to respond to medications, other treatment options include surgery.

Surgical management

Hemispherectomy, lobectomy or transection of the corpus callosum have been described as possible treatments for patients with SWS and medically resistant epilepsy, particularly when associated with clinically significant hemiparesis, visual field loss, and developmental delay.

In refractory cases, hemispherectomy or more limited surgical resection of epileptogenic tissue may be beneficial. The available data suggest that focal resections are less likely to result in good seizure control than hemispherectomy.

Sturge-Weber Foundation conducted a study with 70 patients who had a hemispherectomy between 1979 and 2001. Thirty-two patients (45.7%) responded well to the treatment, 81% of the 32 who responded were free of seizures and 53% were off anticonvulsants.

Clinical management

Epilepsy is one of the most serious symptoms due to its variations. In short, the treatments involved with this symptom are medication such as carbamazepine, vigabatrin, oxcarbazepine, levetiracetam and other types of antiepiletics drugs.
In a retrospective review of 27 children with SWS who had surgery for medically resistant epilepsy, functional or anatomic hemispherectomy was followed by complete resolution of seizures in eight of eight patients; with focal resection, seizure-free outcome was reported in 11 of 19 (58%)⁹.

**REFERENCES**

1. Triana Junco PE, Sánchez-Carpintero I, López-Gutiérrez JC. Preventive treatment with oral sirolimus and aspirin in a newborn with severe Sturge-Weber syndrome. Pediatr Dermatol. 2019; 36: 524–527. doi: 10.1111/pde.13841.

2. Maraña Pérez AI, Ruiz-Falcó Rojas ML, Puertas Martín V, et al. Análisis del síndrome de Sturge-Weber: estudio retrospectivo de múltiples variables asociadas. Neurología. 2017;32(6):363–370. doi: 10.1016/j.neuro.2015.12.012.

3. Nabbout R, Juhász C. Sturge-Weber syndrome. Handb Clin Neurol. 2013;111:315-21. doi: 10.1016/B978-0-444-52891-9.00037-3.

4. 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;28(6):725-31. doi: 10.1177/0887899412451326.

5. Lo W, Marchuk DA, Ball KL, et al. Updates and future horizons on the understanding, diagnosis, and treatment of Sturge-Weber syndrome brain involvement. Dev Med Child Neurol. 2012;54(3):214-23. doi: 10.1111/j.1469-8749.2011.04169.x.

6. Collettini F, Diederichs G, Gebauer B, Poellinger A. Sturge-Weber syndrome. Pediatr Neurol. 2011;47(1):80. doi: 10.1159/000329631.

7. Jiruska P, Marusic P, Jefferys JG, Krsek P, Cmejla R, Sebrnová V, Komarek V. Sturge-Weber syndrome: a favourable surgical outcome in a case with contralateral seizure onset and myoclonic-astatic seizures. Epileptic Disord. 2011 Mar;13(1):76-81. doi: 10.1684/epd.2011.0407.

8. Pascual-Castroviejo I, Pascual-Pascual SI, Velazquez-Fragua R, Viano J. Sturge-Weber syndrome: study of 55 patients. Can J Neurol Sci. 2008;35(3):301-7. doi: 10.1017/s0317167100008878.

9. Bourgeois M, Crimmins DW, de Oliveira RS, et al. Surgical treatment of epilepsy in Sturge-Weber syndrome in children. J Neurosurg. 2007;106(1 Suppl):20-8. doi: 10.3171/ped.2007.106.1.20.

10. Schropp C, Sörensen N, Krauss J. Early periinsular hemispherotomy in children with Sturge-Weber syndrome and intractable epilepsy—outcome in eight patients. Neuropediatrics. 2006;37(1):26-31. doi: 10.1055/s-2006-923945.

11. Comi AM. Advances in Sturge-Weber syndrome. Curr Opin Neurol. 2006;19(2):124-8. doi: 10.1097/01.wco.0000218226.27937.57.

12. Di Rocco C, Tamburrini G. Sturge-Weber syndrome. Childs Nerv Syst. 2006;22(8):909-21. doi: 10.1007/s00381-006-0143-2.

13. Basela E. Sturge-Weber syndrome. Semin Cutan Med Surg. 2004;23(2):87-98. doi: 10.1016/j.sder.2004.01.002.

14. Tuxhorn IEB, Pannek HW. Epilepsy surgery in bilateral Sturge-Weber syndrome. Pediatr Neurol. 2002;26(5):394–397. doi: 10.1016/s0887-8994(01)00414-3.

15. Prayson, R.A. Clinicopathological findings in patients who have undergone epilepsy surgery in the first year of life. Pathology Internat. 2000, 50: 620–625. doi: 10.1046/j.1440-1827.2000.01101.x.

16. Arzimanoglou A, Aicardi J. The epilepsy of Sturge-Weber syndrome: operative indications and surgical results. Brain Dev. 1990;12(5):473-7. doi: 10.1016/s0387-7604(12)80210-5.

17. Bye AM, Matheson JM, Mackenzie RA. Epilepsy surgery in Sturge-Weber syndrome. Aust Paediatr J. 1989;25(2):103-5. doi: 10.1111/j.1440-1754.1989.tb01428.x.

18. Kaplan EH, Kossoff EH, Bachur CD, et al. Anticonvulsant Efficacy in Sturge Weber Syndrome. 2016; 58:31-36. doi: 10.1016/j.pediatrneurol.2015.10.015.

19. Kossoff EH, Buck C, Freeman JM. Outcomes of 32 hemispherectomies for Sturge-Weber syndrome worldwide. Neurology. 2002;59(11):1735-8. doi: 10.1212/01.wnl.0000035639.54567.5c.

**CONCLUSION**

Both clinical and surgical treatment showed effectiveness in the management of SSW. A major unanswered question is whether suppression of seizures by aggressive treatment with antiepileptic drugs or surgery early in the disease development would prevent future neurological symptoms and cognitive decline.
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