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Updates in Medication for Sturge-Weber Syndrome: A Mini Review

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Abstract

Sturge-Weber Syndrome is a rare neurovascular disease associated with glaucoma, a port wine birthmark and most commonly, leptomeningeal vascular malformations accompanied by medically refractory epilepsy. Due to the poorer prognosis associated with extensive brain involvement and early onset of seizures, aggressive and early diagnosis and seizure treatment remains a focus. The past decade has produced a base of literature published on studies and trials for interventions to treat and manage these devastating symptoms. This mini-review focuses on a recent multi-centered study of patient reported medications for SWS and on three other recent treatment trials for SWS: the use of the mTOR pathway inhibitors Sirolimus, a trial with Epidiolex (cannabidiol), and presymptomatic treatment of SWS. An overview of treatment progress for patients with SWS, can be beneficial for clinical providers and patients to determine alternative ways of management.

Keywords: Sturge-Weber syndrome; Sirolimus; Seizures; Epilepsy; Anti-seizure medication; Cannabidiol; Presymptomatic

Introduction

Sturge-Weber Syndrome (SWS) is a non-inherited neurovascular disease associated with a port- wine birthmark, glaucoma, and leptomeningeal capillary venous malformation resulting in supratentorial hemisphere atrophy and brain injury in most cases. The disease is caused by an activating somatic mutation in the gene GNAQ, encoding the $G_{\alpha q}$ subunit [1]. The neurological symptoms of Sturge-Weber syndrome occur at variable severity, largely due to varying extent of brain involvement [2]. The neurological manifestations of SWS can often result in cerebral atrophy, seizures, acquired hemiparesis, and varying degrees of intellectual disability [2]. Approximately 75% up to 90% of patients with SWS brain involvement will develop epilepsy, mostly during the first year of life [3]. Poorer prognosis is indicated by extensive brain involvement and early onset of seizures, therefore, early diagnosis and aggressive treatment of symptoms remains the priority in management of this syndrome [4]. With the emphasis placed on early and aggressive seizure treatment, there is a demand for a comprehensive evaluation of recent literature on both pre and post-symptomatic treatment. This review aims to identify updated methods of treatment and management of the debilitating neurological consequences of Sturge-Weber syndrome.

Medication for Epilepsy

According to the multi-centered study conducted by Smegal et al., levetiracetam, oxcarbazepine and low-dose aspirin were the most commonly used medications to treat epilepsy in patients with SWS. This study involved the analysis of questionnaires answered by 312 patients diagnosed with SWS and their families. Out of this population, 268 patients reported having a history of seizures. 48.1% of respondents with a history of seizures were on levetiracetam, 29.9% were on oxcarbazepine and 44.8% were on low-dose aspirin. Levetiracetam and oxcarbazepine were not only the more common anti- epileptic medications used in patients with SWS and epilepsy but they were also reported to be the most common combination. Phenobarbital and lacosamide were commonly used as adjuvant therapy. Low- dose aspirin was used in almost half of the patients that completed this survey with a history of seizures and was associated with younger age of enrollment [5]. Not only has low-dose aspirin been beneficial to patients treated symptomatically, there are reports of potential applicability to presymptomatically treated patients [6].

Past research has suggested that patients that experience refractory seizures that are unresponsive to anticonvulsant medication may turn to surgical options [7]. Surgery is recommended primarily to patients with unilateral brain involvement and that have failed two or more seizure medications along with aspirin. Levetiracetam and oxcarbazepine were also the most common anti-epileptic medications taken by participants that had a history of brain surgery and continued on anti-epileptic medication therapy. Out of the twenty-eight respondents that have reported a history of brain surgery, only one respondent had bilateral brain involvement. This participant continued on phenobarbital. A history of brain surgery was associated with being off seizure medications at the time of the survey [5].

Along with the respondents that were children, there were 37 adult participants with SWS with a history of seizures. Six of these patients (16%) were not using seizure medications at the time of the survey, suggesting that some patients may be able to wean off of seizure medications. Not being on a seizure medication, as an adult with a prior seizure history, was significantly associated with female sex and

a unilateral port-wine birthmark. Levetiracetam and lamotrigine were the most used seizure medications in adult respondents.

This analysis of the largest multicenter registry of patients with SWS is indicative of consensus on the use of levetiracetam, oxcarbazepine and low-dose aspirin to be favorable in the treatment of seizures. More research is needed to identify early those patients who fail these medications, and which will be best treated by early surgery, the ketogenic/Atkins diet, VNS, and other medications.

Epidiolex

Currently, ongoing research is attempting to identify the exact mechanism that causes the somatic mutation of GNAQ to result in the malformation of blood vessels. It is likely that this mutation causes an over-activation of the Ras-Raf-MEK-ERK-mTOR pathway resulting in an increase in VEGF and HIF activities. Consequentially, this to results in abnormal leptomeningeal vessels and vascular remodeling contributing to the occurrence of the port wine birthmark, glaucoma and seizures. Recently, research has suggested that cannabidiol may have anticonvulsant effects. It has been proposed that, amongst other mechanisms, CBD blocks the mammalian target of the mTOR pathway and displays anti-inflammatory effects. There has been extensive research on the use of CBD for various pediatric epilepsies. Kaplan et al. studied the safety and efficacy of CBD for medically refractory seizures in SWS. This trial involved five subjects with SWS related brain involvement and severe medically refractory epilepsy. The results of this trial showed a significant decrease in seizure frequency, improvements in quality of life, and subjective improvements in fine and gross motor, speech and cognitive ability. From the five subjects in the trial, three with bilateral brain involvement responded the most to CBD. The remaining two were removed due to lack of efficacy. One of these subjects previously underwent a focal surgical resection.

Additionally, one subject was withdrawn due to a temporary increase in seizures during dose titration and was re-enrolled and increased to a 5 mg/kg/day dose. This patient was enrolled at the age of 19 and was the oldest subject. These results suggest that CBD may be a beneficial treatment for the refractory seizures that plague patients with Sturge-Weber syndrome [8].

Sirolimus

The hyper-activation of the mTOR pathway that is consequential of SWS is a common target for therapeutic drugs. Sirolimus, a mTOR inhibitor, has shown to be a beneficial treatment to improve cognitive function, quality of life and outcomes caused by ischemic brain occurrences. In a study conducted by Sebold et al., the safety and change in cognitive function of sirolimus was investigated in 10 subjects with SWS brain involvement and cognitive impairment. There was significant improvements between the baseline and 6 month follow up testing in processing speed, and in the quality of life domains of anger, depression and cognitive function. It was determined that sirolimus was tolerated well by most subjects in the study; however the safety of sirolimus in patients with bilateral SWS brain involvement requires further study. Though these results are positive, the full extent of the impact of sirolimus on cognitive impairment in SWS will need to be investigated by a prospective, randomized placebo- controlled trial [9].

Discussion

In the past, research has focused primarily on the post-symptomatic treatment and management of Sturge-Weber syndrome. As previously described, aggressive seizure management, following the onset of seizures typically involves the use of anti-epileptic medication and/or low-dose aspirin; when medication fails then surgery, the diet, and VNS should be considered. In Day et al., it is hypothesized that the presymptomatic use of anti-epileptic medication and low-dose aspirin could have the potential to delay age of seizure onset. In this study, thirteen presymptomatically treated subjects (5 aspirin only and 8 aspirin plus seizure medication) were compared to post-symptomatically treated patients that were matched by gender, extent of brain involvement and age. The SWS neurological score and age of seizure onset were compared. The analysis of the subjects presymptomatically treated with aspirin and anti- epileptic medication were showed to have a significantly lower seizure score as compared to their post- symptomatically treated counterparts. Additionally, the age of seizure onset for the presymptomatically treated subjects was higher at the time of analysis. These findings also suggested that presymptomatic treatment is most beneficial for patients with extensive brain involvement. This hypothesis provides the framework indication for future studies focused on neuroprotective interventions to delay or prevent seizure onset in patients with SWS [6].

Conclusion

Sturge-Weber is a devastating disease that is accompanied with the debilitating occurrence of refractory seizures. Without intervention, 75% of children with Sturge-Weber related brain involvement will develop seizures within the first year of life. This prognosis, along with the worse neurologic outcome associated with early onset of seizures, emphasizes the focus on research for targeted and aggressive seizure treatment. As research continues, data supports therapeutic interventions targeting the mTOR pathway and other downstream effects of the GNAQ mutation. The potential for both pre and post-symptomatic drug intervention provides encouragement in developing drug trials to test safety and efficacy. This progress brings along hope of seizure relief, and improved neuro-cognitive outcome for patients with SWS.

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