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Original article

The natural history of pediatric Sturge-Weber Syndrome: A multinational cross-sectional study

Sigrid Claudia Disse [a,b,*], Hanna Küpper [c], Annette Bock [d], Georg-Christoph Korenke [e], Georgia Ramantani [f], Birgit Weidner [g], Martin Preisel [h], Regina Trollmann [i], Adelheid Wiemer-Kruel [j], Knut Brockmann [k], Simone Schroeder [k], Sascha Meyer [l]

[a] University Children's Hospital Regensburg (KUNO) – Hospital St. Hedwig of the Order of St. John, University of Regensburg, 93049, Regensburg, Germany
[b] Children's Hospital at University Medical Center, Homburg, Germany
[c] University Children's Hospital, Tübingen, Germany
[d] University Hospital, Essen, Germany
[e] Department of Neuropediatrics, University Children's Hospital, Klinikum Oldenburg, Oldenburg, Germany
[f] University Children's Hospital, Zürich, Switzerland
[g] Pediatric Practice, Cottbus, Germany
[h] University Hospital, Salzburg, Austria
[i] Pediatric Neurology, University Children's Hospital Erlangen, Germany
[j] Pediatric Epilepsy Center Kehl-Kork, Germany
[k] University Medical Center Göttingen, Germany
[l] Franz-Lust Klinik für Kinder und Jugendliche, Karlsruhe, Germany

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ABSTRACT

Background: Sturge-Weber Syndrome (SWS) is a capillary-venous malformation which includes the brain (leptomeningeal venous capillary malformation), the eye (choroidal angioma) and the skin (facial portwine birthmark, FPB). Structural epilepsy, glaucoma and FPBs pose therapeutic challenges. Considerable advances include improved neuroimaging, new antiseizure medication (ASM) and progress in epilepsy surgery. Yet, comprehensive data on epidemiology, clinical features, diagnostics, and treatment in contemporary pediatric SWS cohorts is scarce.

Methods: We conducted a multinational cross-sectional observational study in Germany, Switzerland and Austria to identify potential patients and build up a comprehensive database containing anonymized patient data. The patients' guardians and child neurologists filled in detailed questionnaires on histories, clinical features, diagnostic and therapeutic measures.

Results: Forty-seven SWS patients from Germany, Switzerland or Austria participated in our survey (111 notifications, i.e. the participation rate was 43 %). Prevalence was 7.37/million in Germany, 4.60/million in Switzerland, 2.61/million in Austria. Severity of skin, eye and brain involvement varied highly. Forty-three patients (91 %) were diagnosed with epilepsy. Median age at first seizure was 6.5 months. Thirty-two percent of the cohort received ASM in monotherapy, fifty-three percent received combination therapy and thirteen percent received no ASM. Eight percent underwent epilepsy surgery.

Conclusions: In this European pediatric SWS cohort from a well-established tertiary child neurologist network, the condition was commonly diagnosed within the first year of life. 40 % of the cohort were seizure-free at inclusion;

Abbreviations: ASM, antiseizure medication; CNS, central nervous system; CI, confidence interval; EEG, electroencephalogram; ESNEK (German "Erhebung Seltener Neurologischer Erkrankungen im Kindesalter", English translation "Survey of Rare Neurological Disorders in Childhood"); FPB, facial portwine-birthmark; LTG, lamotrigine; LEV, levetiracetam; MRI, magnetic resonance imaging; OXC, oxcarbazepine; PHACE Syndrome, Syndrome which includes Posterior fossa brain malformation, (usually facial) Hemangioma, Arterial Anomalies, Cardiac anomalies, Eye abnormalities; SWS, Sturge-Weber Syndrome.

* Corresponding author. University Children's Hospital Regensburg (KUNO) – Hospital St. Hedwig of the Order of St. John, University of Regensburg, 93049, Regensburg, Germany.

E-mail addresses: sigrid.disse@barmherzige-regensburg.de (S.C. Disse), Hanna.Kuepper@med.uni-tuebingen.de (H. Küpper), annette.bock@t-online.de (A. Bock), korenke.georg-christoph@klinikum-oldenburg.de (G.-C. Korenke), Georgia.Ramantani@kispi.uzh.ch (G. Ramantani), weidner@kinderaerzte-cottbus.de (B. Weidner), m.preisel@salk.at (M. Preisel), regina.trollmann@uk-erlangen.de (R. Trollmann), adelheid.wiemer-kruel@freenet.de (A. Wiemer-Kruel), knut.brockmann@med.uni-goettingen.de (K. Brockmann), simone.schroeder@med.uni-goettingen.de (S. Schroeder), Sascha.Meyer@klinikum-karlsruhe.de (S. Meyer).

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only 8.5 % of the cohort underwent epilepsy surgery. Our findings are concordant with published data from U.S. registries and case series. While our results indicate diagnostic improvement as compared to published studies, epilepsy management in SWS remains a challenge.

1. Introduction

Sturge-Weber Syndrome (SWS) is a rare congenital disorder (OMIM # 185300) [1], which typically presents with a facial vascular birthmark, glaucoma and seizures. The hallmark of SWS is a leptomeningeal capillary-venous malformation of the brains, usually detected on contrast-enhanced T1 weighted MRI imaging (formerly often referred to as leptangiomatosis). The condition SWS was first described in 1879 in a 6.5 year-old girl with an extensive facial birthmark, buphtalmos and focal seizures with secondary generalization [2]. Intracranial calcifications were detected only in 1922 by X-rays [3,4]. A somatic activating mutation in a G-protein was identified in 2013 [5] as the molecular basis of this multisystem disease, providing insight into the involved cellular pathways. The discovery of this mutation and another somatic mutation in the same G-protein complex [6] are potential targets for novel therapeutic strategies. However, structural epilepsy, cognitive impairment, stroke-like episodes and behavioral problems still pose therapeutic challenges [7].

SWS is estimated to affect 1 in 20,000 to 50,000 livebirths [8,9]. Previous pediatric/adolescent cohorts and case series reported small sample sizes with ≤20 affected patients [10–28] and/or were limited to SWS subgroups [10–35] selected according to comorbidities, diagnostic procedures, pathogenesis, treatment and factors prognostic of cognitive and psychological function as well as psychomotor development. The available larger pediatric studies in 44–237 pediatric patients focused on electroencephalogram (EEG) evolution [36], aspirin use [31], focal glucose hypermetabolism in PET scans [34], psychosocial functioning [29], headaches [37], transient hemiparesis [38], and predictors of cognitive development and neurological deficit [39]. Few studies investigated the outcomes of epilepsy surgery in SWS; among these, a large retrospective, European multicenter cohort which included 36 SWS patients [40]. Some SWS studies included both children and adults, but the number of pediatric patients was not explicitly stated in all studies [32,41–43]. The largest recent database with SWS patients in terms of sample size and number of included clinical features derived from U.S. registry data, including online questionnaires filled in by 628 survey participants [44]. The survey covered a large age spectrum, as both the age at diagnosis and the age at occurrence of first symptoms indicated by study participants ranged from “birth” to “70 years”; it should, however, be noted that the included data was purely patient-reported.

To the best of our knowledge, no population-based pediatric SWS cohorts have been reported so far. Moreover, contemporary population-based data on the pediatric SWS prevalence in Europe are missing. Given the highly varying disease manifestations between different patients, in-depth clinical and epidemiological characterization of a larger set of individual patients may be a first step towards precision medicine in this rare disease.

We drew from a well-established network of child neurologists [45] to create a comprehensive database with detailed data on demographics, clinical features, diagnostic and therapeutic approaches applied in children with SWS residing in Germany, Switzerland or Austria.

2. Materials and methods

2.1. Study overview

We used a network of child neurologists (“ESNEK”, i.e. in German “Erhebung Seltener Neurologischer Erkrankungen im Kindesalter” [45]; engl. “Registry of Rare Neurological Disorders in Childhood”) to conduct a multinational survey in the three German-speaking countries Germany, Switzerland and Austria. In a parallel study arm, we had previously assessed data on another, less well-known phacomatosis, PHACE Syndrome, to identify potentially confounded cases [46]. PHACE Syndrome may include different malformations summarized in acronym PHACE- Posterior fossa brain malformation, (usually facial) Hemangioma, Arterial Anomalies, Cardiac anomalies, Eye abnormalities. The detailed study methods and the basic principles of the ESNEK network are given in this publication [46]. For the present study, we included all patients with a definitive clinical diagnosis of SWS. Among collaborating child neurologists, 49 notified us of SWS patients in their care; ten patients were self-recruited through the German SWS support group or by referral through other patients, and their diagnoses were verified by our study team. The study protocol was approved by the responsible Institutional Review Board in Saarbrücken, University of Saarland, Germany (ID 209/17, October 2017). In 44 cases, the patients’ legal guardians provided informed consent. Three cases were sent anonymously by their attending child neurologists. The study was registered in the German Clinical Trials Registry (ID: DRKS 00013551, UTN U1111-1206-9923).

2.2. Case definition and inclusion criteria

We used the widely accepted SWS criteria by Roach et al. [47] and enrolled patients with SWS types I-III. We recorded atypical cases of SWS, i.e., overlap with other phacomatoses or presence of systemic capillary-venous vascular malformation. We included all patients aged <18 years who currently live in Germany, Switzerland or Austria. Study enrolment started in January 2018 and lasted until December 2018; recruitment ended in June 2019. We included each case which completed the questionnaire actively participated in our study only after verification of medical records and/or questionnaires.

2.3. Data assessment

We used two modified versions of our previously described questionnaires from our PHACE Syndrome Study [46]. One questionnaire was adapted for parents, and one for child neurologists. The parental questionnaire comprised questions on patients’ demographics, family history, birth and prenatal history, ethnicity, current symptoms including descriptions of skin and organ involvement, hearing, feeding, language skills, neurocognitive development, and use of health services. The child neurologists’ questionnaire included questions on SWS-specific organ involvement – under consideration of recent findings [43]-, family history, birth and prenatal history, current symptoms including components of SWS clinical severity scores [18], description of skin involvement, further organ involvement, diagnostic procedures incl. genetics, therapies and therapeutic success, including the use of ASM and epilepsy surgery. Clinical severity scores (adapted from Refs. [18,43]) comprise the severity of visual field defect, hemiparesis, seizure frequency and cognitive function, were calculated from the child neurologists’ questionnaires. As paper questionnaires allowed users to skip questions, we formally handled some missing data as normal values in the section on SWS clinical severity scores, if this section was otherwise complete and the given values medically plausible (see exemplary case in the appendix). We used a previously [48] demonstrated cut-off value to distinguish between intellectually impaired patients (score ≥4) and non-impaired patients (score <4; sensitivity 75 %, specificity 65 %).

For some questionnaire items, we have to acknowledge missing data as follows: epileptic seizures during lifetime (n = 1), paresis (n = 3), need of visual aid (n = 5), laterality of FPB (n = 3), data on neuroscore

incomplete and thus not included (n = 12). Data on cerebral atrophy in cerebral MRI not explicitely documented (n = 5), on EEG diagnostics (n = 1), and some questionnaires lacked a formal diagnosis of developmental status/delay (n = 6).

2.4. Statistical methods

We used RStudio, version February 1, 1335 for data analysis [49] If normally distributed, we indicated mean/standard deviation to describe continuous variables, and median/interquartile ranges for other distributions. For categorical variables, absolute and relative frequencies are given. Correlations were analyzed with spearman rank correlation coefficients, as the respective covariates were not normally distributed. We also indicated 95 % confidence intervals (CI) of correlation coefficients to correct for sampling errors (package "psychometric"). We applied standard epidemiologic procedures for the calculation of the disease prevalence. The required population data for Germany, Switzerland and Austria were extracted from public electronic databases [50–54]. We used midyear populations under risk to calculate the disease prevalence in order to minimize error due to changes in the population occurring during the course of a year. As the assumptions of independent disease occurrence and homogeneity of risks for the individual patients were fulfilled, we used a binomial distribution to determine confidence intervals of the prevalence values [55]. For the latter confidence intervals, we used the BinomCI function from the "DescTools" package to calculate Wilson score test-based confidence intervals. To explore the impact of aspirin therapy, we conducted an exploratory post-hoc analysis. We used Benjamini Hochberg procedure to adjust for multiple testing (11 tests).

3. Results

3.1. Patient characteristics

We handled 111 notifications of non-related pediatric patients with clinically diagnosed Sturge-Weber Syndrome (after correction for duplicates). Forty-seven patients and/or child neurologists consented to participate in our associated survey and completed the dedicated questionnaires (response rate 43.2 %).[1] In all patients, we critically reviewed the questionnaires filled in by families and pediatricians/child neurologists, and all questionnaires of all patients showed sufficient data quality for inclusion into our study. In 17 cases, we received patients' photographs of their SWS-specific birth marks (34.0 %). Among 47 patients, 39 reside in Germany, 4 in Switzerland and 4 in Austria. Twenty-five patients were male, 22 patients were female (ratio m/f = 1.13). The age at study inclusion ranged from 115 days to 17.5 years (median 4.2 years). The demographic characteristics of the study cohort are summarized in Table 1. Using the classification by Roach [47], 35 patients fulfilled the criteria for a "classical" Sturge-Weber Syndrome type I (74.5 %), and 6 for type III (12.8 %). Four cases were atypical (8.5 %) due to additional symptoms typical of Klippel-Trénaunay Syndrome (n = 2; i.e., "overlap phacomatoses"), additional cerebrovascular anomalies with only mild leptomeningeal capillary-venous malformations (n = 1), or additional hemangioma of the trunk (n = 1). One case was classified as both systemic capillary-venous malformation with the full characteristics of SWS type I and Klippel-Trénaunay Syndrome. Another case displayed signs of systemic capillary-venous malformation (2.1 %). Among the patients with notification-only (data not included due to non-participation), 4 patients fulfill the criteria for SWS type II (isolated skin involvement).

[1] One questionnaire for the child neurologist was completed by the patient's mother who is an experienced nurse.

Table 1
Patient demographics at time of study inclusion.

Patient characteristics (n = 47)	N (%)
Sex	
- Male	25 (53.2 %)
- Female	22 (46.8 %)
Current age in years, median (IQR); range	4.2 (1.9–9.0); 4 months-17.5 years
Age at first diagnosis in months, median (IQR); range	5.0 (0.2–9.0); 0 months–24 months
Race *(not reported = 15)*	
- Caucasian	30 (90.9)
- Asian/Arab	2 (6.1)
- African (mother)	1 (3.0)
Country	
- Germany	39 (83.0)
- Austria	4 (8.5)
- Switzerland	4 (8.5)
Sturge Weber Syndrome Type (Roach, 1992)	
- Type I	35 (74.5)
- Type II	0 (0)
- Type III	6 (12.8)
- Atypical cases	4 (8.5)
- Systemic capillary-venous malformation	2 (4.3)

3.2. Prevalence of SWS in Germany, Switzerland and Austria

We calculated the disease prevalence in the three countries based on the total number of notifications we received by the child neurologists from the ESNEK network, independent of the patients' study participation. The prevalence was 7.370/million [95 % CI 6.060; 8.963/million] in Germany; 4.602/million [95 % CI 2.229; 9.500/million] in Switzerland, and 2.608/million [95 % CI 1.014; 6.707/million] in Austria.

3.3. Diagnostic procedures

All patients received a comprehensive diagnostic workup including cerebral imaging studies, electroencephalography (100 %) and ophthalmologic evaluation (100 %; see Fig. 1). Formal developmental tests were reported in 16 patients-approx. one third of the cohort although developmental delay was reported in 63.8 % (30/47). Genetic consultation was rarely performed (7/47, 14.9 %), resulting in genetic testing in 2 cases (4.2 %). Genetic testing involved GNAQ mutation in one patient, and SNP array and whole exome sequencing in blood in the other; in both cases, with overall negative results.

The diagnosis, as reported by parents/caregivers, was made within the first year of life in 82.9 % of patients and in 100 % within the first two years (range: birth – 24 months; median 5.0 months; 12.8 % missing values). Approximately one quarter (26.8 %) of parents reported a diagnosis in the neonatal period (n = 13/47). Most patients (36.2 %, n = 17/47) were diagnosed in a children's hospital or, if specifically stated, by a child neurologist (21.3 %, n = 10/47). In few cases, the diagnosis was first established by a radiologist (4.2 %, n = 2/47) or a dermatologist (2.1 %, n = 1/47). Fig. 2 (online-only supplement) shows the cumulative age distribution at first diagnosis. We recorded no further data on diagnostic circumstances.

In 38.3 % (18/47) of patients, the latency between age at first diagnosis and age at first seizure was ≤4 weeks, indicating coincidence of the events, and age at first seizure and age at first diagnosis showed a significant correlation (rho 0.65, 95 % CI 0.44; 0.79). In 12.8 % (n = 6/47) patients, the diagnosis was established several months prior to the seizure onset (up to 13 months; another 4 patients have remained seizure-free). On the other hand, 12.8 % patients were diagnosed with SWS ≥4 weeks after the first seizure. Age at first seizure was reported in 72.3 % of patients (n = 34/47) and ranged from two days to 20 months (median 6.5 months). Seizure onset within the first year of life occurred in 78.1 % of our cohort. Fig. 3 compares ages at first seizure and at SWS

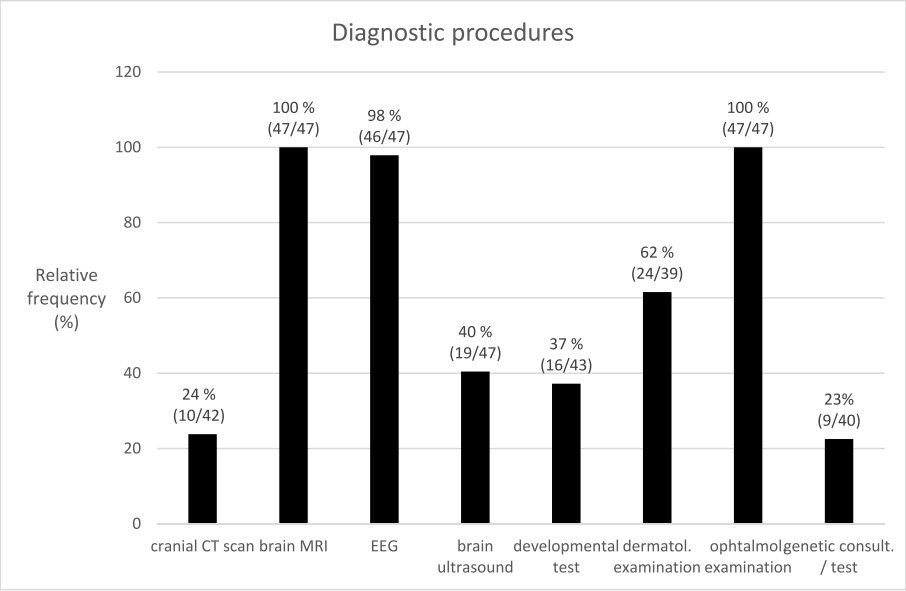

Fig. 1. Overview of diagnostic workup in SWS patients of this cohort at time of study inclusion. Multiple responses were possible. Difference to 47 in the denominator is due to missing data (denominator refers to total number of respondents in this category).

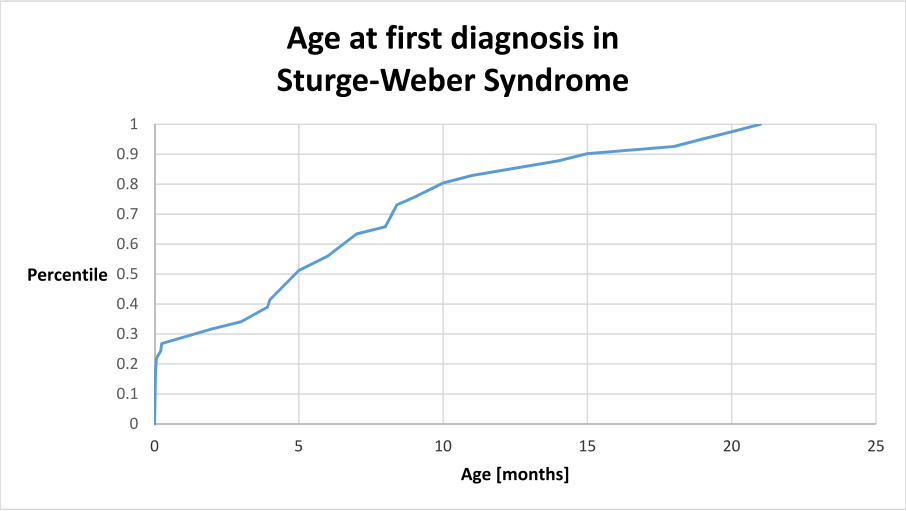

Fig. 2. (online-only supplement): Cumulative distribution of age at first diagnosis in our pediatric SWS cohort.

diagnosis.

3.4. Clinical characteristics

The clinical features are described in detail in Table 2. The majority of patients had epileptic seizures at any time during their lifetime (91.5 %, 43/47). Paresis (clinical severity score ≥1) was diagnosed in 60.0 % of cases (28/47) Occurrence of glaucoma during lifetime was indicated in 44.7 % (21/47) of cases, including a need of a visual aid in 34.0 % (16/47). Skin manifestations of SWS in terms of a facial portwine-birthmark (FPB) presented unilaterally in 53.2 % (25/47), and bilaterally in 27.7 % (13/47) cases. No FPB was noted in 12.8 % (6/47), compatible with type III SWS (Roach, 1992). Hence, 21.3 % of patients (10/47) can be classified as "non-impaired", 53.2 % patients (25/47) as "impaired". Exploratory analyses showed that clinical severity scores showed low, positive correlations with the number of ASM (rho = 0.369, 95 % CI 0.092; 0.593) and with age at inclusion (rho = 0.349, 95 % CI 0.069; 0.578).

3.5. Magnetic resonance imaging findings

Cerebral atrophy was frequently detected in neuroimaging (74.5 %, 35/47)- and it was earliest described in a neonatal magnetic resonance imaging (MRI). Leptomeningeal capillary-venous malformation occurred in 100 % (47/47)*[2] and was described earliest at the age of 6 months in the MRI- in a patient with SWS Roach Type III.

3.6. ASM therapy and treatment success

The median number of concurrently administered ASM was 2.0 (range 2–4). Monotherapy was recorded in 15 patients (31.9 %): levetiracetam (n = 10, LEV), oxcarbazepine (n = 3, OXC) and lamotrigine (n

[2] In one patient, original MRI finding was not provided by the attending child neurologist and it was not available to the patient's parents. However, the patient's mother reported that a formal diagnosis of SWS was made by an experienced child neurologist and that cerebral MRI was pathologic.

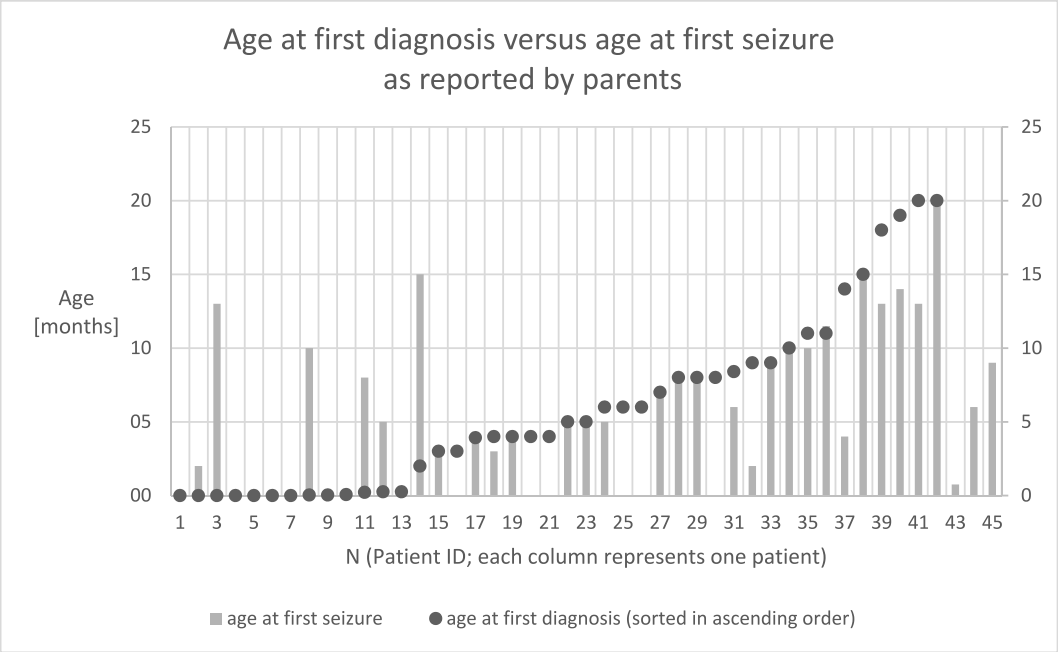

Fig. 3. Cumulative distributions of age at first diagnosis in months versus age at first seizure as reported by parents/caregivers.

= 2, LTG). During the time of study conduct, one patient was switched to ASM monotherapy with LEV and additional ketogenic diet. In most patients with monotherapy, the referring child neurologist reported the treatment success as "good" (LEV: n = 8/10; OXC: n = 2/3); in two cases, treatment success was reported as moderate (n = 1, LTG, and OXC, respectively). At study inclusion, six patients (12.8 %) were reported to receive no ASM. A subgroup analysis showed that one of these six patients was seizure-free with aspirin prophylaxis only and another was seizure-free following hemispherotomy; a third patient never suffered from any seizures and was given no medication. Three further patients without medication were seizure-free at study-inclusion and also received no ASM (all SWS type 1, ages 3-10y). 25 (53.2 %) patients had ASM combination therapy. Overall, 17 different ASM were used (Fig. 4, online-only supplement) in 20 different combinations. The only combinations used in more than one patient were LEV + OXC (n = 4) and OXC + valproate (n = 2).

The most widely used ASM were: LEV (n = 19), OXC (n = 16), valproate (n = 15), LTG (n = 11), and phenobarbital (n = 6). The treatment success rates of different ASM in combination therapy is displayed in Fig. 5.

3.7. Treatment with aspirin

Aspirin was administered to 21 of 47 patients (44.7 %). There was no significant difference between patients with vs. without aspirin therapy with regard to age at first seizure, age at diagnosis, current seizure frequency and number of currently administered ASM. Stroke-like episodes (3 vs. 5) and cases with severe or significant paresis (7 vs. 10) were numerically lower in the aspirin group but the finding was not statistically significant. Overall SWS neuroscores did not differ between the two groups. We recorded *more* cases with cerebral calcifications under aspirin therapy than without (12 vs. 5, p = 0.032). The finding did not remain significant after adjustment for multiple testing. Two patients with current aspirin therapy were evaluated for surgery earlier; all operated patients received no aspirin. In this study, we did not assess side effects of treatment with aspirin. Details on the comparative analysis are presented in online-only Table 3.

4. Discussion/conclusions

This study provides detailed clinical data on SWS in children in Europe from a multinational tertiary child neurologist network. We report the estimated disease prevalence, the current state of diagnostics, describe the clinical spectrum, current treatment approaches and therapeutic success in a large, multinational pediatric SWS cohort.

4.1. SWS prevalence

The prevalence values calculated in this study varied between 2.6 and 7.4 per million, with overlapping confidence intervals between Germany, Switzerland and Austria. Rihani et al. reported an age- and sex-adjusted annual incidence rate of 1.9 per million in Olmsted, Minnesota [57], based on 13 SWS cases diagnosed over a 17-year period. Yet, given the fundamental differences between prevalence and incidence rate [58], comparability is limited. According to Orphanet recommendations [59]- "point prevalence is considered the most appropriate epidemiological indicator for rare diseases" [60]. Yet, two frequently cited previous publications on SWS prevalence state that "no good population data exists, but estimates range between one in 20.000–50.000 live births" [8,61]. Orphanet indicates an SWS prevalence of 10–90 per million [62], and a birth prevalence of 35 per million [63] (Orphanet Summary; last update January 2022). The prevalence can be calculated from the birth prevalence for congenital diseases if the condition's life expectancy is known[3] [63]. We acknowledge the following potential sources of bias which may lead to a potential underestimation of the SWS prevalence in our study- (1) Reporting bias: We recruited the current cohort through a *child neurologists'* network, and thus, only cases with central nervous system (CNS) involvement were reported, likely resulting in underreporting of cases with isolated skin or eye involvement. Thus, we cannot rule out a selection of more severely affected patients. Reporting bias may have occurred as well due to non-reported cases, as ESNEK is a non-mandatory reporting system. In

[3] For congenital diseases, Orphanet estimates prevalence from the birth prevalence as follows: prevalence = birth prevalence x (patient life expectancy/general population life expectancy).

Table 2
Clinical features in the our SWS cohort including skin involvement, cerebral imaging results, epilepsy characteristics, eye involvement, overall clinical severity score and functional impairment including developmental delay, speech delay and requirement of supportive measures. Difference to 47 in the denominator is due to missing data (denominator refers to total number of respondents in this category).

Clinical Features (n = 47)	N (%)
Skin involvement:	
- none	6 (12.8)
-unilateral facial birthmark	25 (53.2)
-bilateral facial birthmark	13 (27.7)
-frontal placode involved, acc. to [56]	28/38 (73.7)
-number of skin segments involved:	
−0	6/43 (14.0)
- 1-4	11/43 (25.6)
-5-8	17/43 (39.5)
-9-11	9/43 (20.9)
Cerebral imaging:	
-leptomeningeal capillary-venous malformation	46/46 (100)
-cerebral atrophy	35/42 (83.3)
-cerebral calcifications	18/43 (41.9)
Structural epilepsy	
-any seizures lifetime	43/46 (93.5)
-developmental delay	30/41 (73.2)
-hemiparesis (score ≥1)	28/44 (63.6)
-stroke/str.-l. episode	8/47 (17.0)
-stroke/str.-l.-episode with residues	5/47 (10.6)
Eye involvement:	
-congenital glaucoma	14/45 (31.1)
-glaucoma during lifetime	20/47 (42.5)
-use of visual aid	16/42 (38.1)
-surgical therapy required	13/42 (31.0)
Clinical Severity Score, adapted from [18,43]	
Score <4	10/37 (27.0)
Score ≥4	25/37 (67.6)
Impairment and requirement ofSupportive measures	
- feeding difficulties	13/41 (31.7)
-Developmental delay	
-none = 0	11/41 (26.8)
-slight = 1	12/41 (29.3)
-moderate = 2	6/41 (14.6)
-severe = 3	12/41 (29.3)
-unknown = 4	6/41 (14.6)
-Speech development delayed	
-no delay	17/38 (44.7)
-isolated articulation difficulties	1/38 (2.6)
-combined, non-severe speech disorder	1/38 (2.6)
-no speaking/autistic	5/38 (13.3)
-severe, complex speech disorder	11/38 (28.2)
-too young for adequate assessment	3/38 (7.9)
Supportive measures	
-requires physical therapy	34/45 (75.6)
-requires occup. therapy	25/46 (54.3)
-requires speech therapy	19/37 (51.4)

another reporting network for Rare Diseases in Germany (not restricted to neurologic conditions), the German Pediatric Surveillance Unit (ESPED), completeness of registration estimates calculated through capture-recapture methods, range between 60 % for Kawasaki Disease [64], and 83–85 % for diabetes mellitus in children [65]. Differences between the countries could be due to underreporting in Switzerland and Austria-as the surveillance system we used is centered in Germany. However, in our previous study on PHACE Syndrome this was not the case [46] as most PHACE Syndrome cases in that previous study were reported from Switzerland. The "true" prevalence of SWS in the German-speaking countries has never been systematically assessed before thus we could not conduct capture-recapture analyses. (2) Diagnostic bias may result from undiagnosed cases in childhood/adolescence which – given the normal life expectancy in SWS [66]- are only identified in adulthood and would result in higher cumulative pediatric and adult prevalence estimates compared to prevalence values from purely pediatric studies. This is supported by data from a U.S. registry, in which only 85 % of cases were diagnosed at age <18 years (other 15 % of cases includes patients >18 y and missing data) [44]. Nevertheless, our estimates are comparable for the three German-speaking countries, and they may serve as a valuable foundation for future follow-up studies.

4.2. *Age at diagnosis and age at seizure onset*

A timely diagnosis is one of the main challenges in SWS. In the large U.S. SWS Registry Study including 628 patients enrolled over a 19-year period, 16 % received "delayed" diagnoses, defined by the authors as a latency period of ≥1 year between symptom onset and diagnosis [44]. These cases were only diagnosed following the onset of severe ophthalmologic or neurologic symptoms of SWS- despite the presence of other neurologic, ophthalmologic, otolaryngologic and/or behavioral symptoms. Both in the study by Cho et al. [44] and in our own clinical experience (SD, not included in this study) delayed diagnosis may occur in children with FPB. This finding highlights the need to counsel caregivers and practitioners on current recommendations for diagnostics in

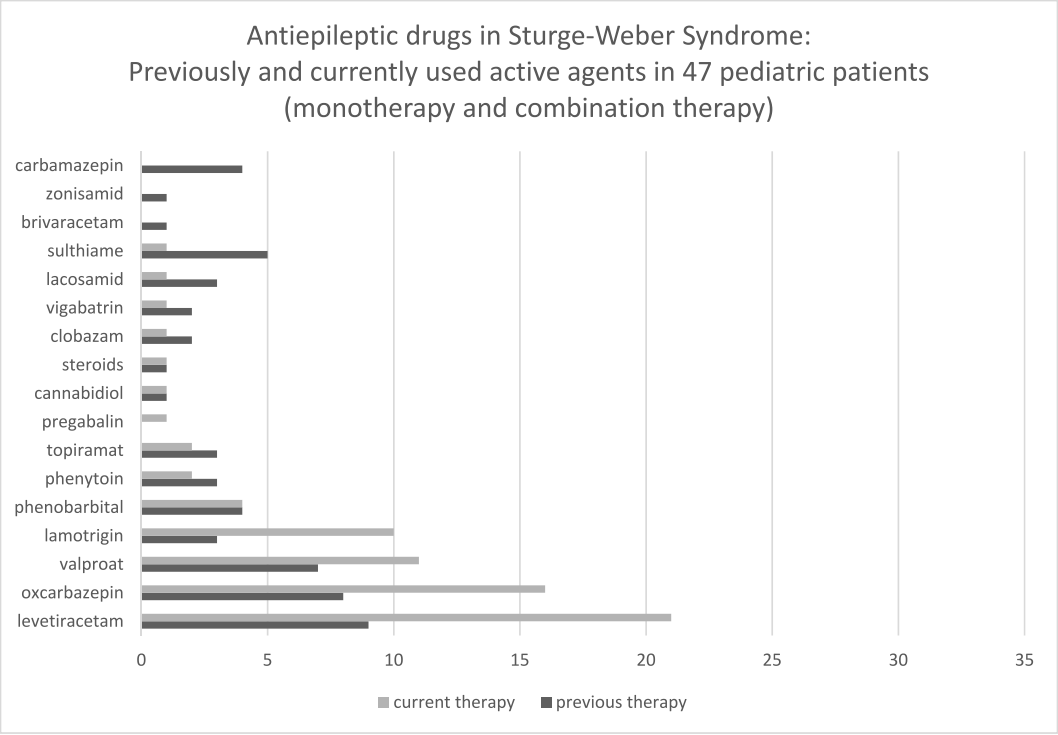

Fig. 4. (online-only supplement): Overview of previously used and currently administered antiseizure medication (monotherapy and combination therapy).

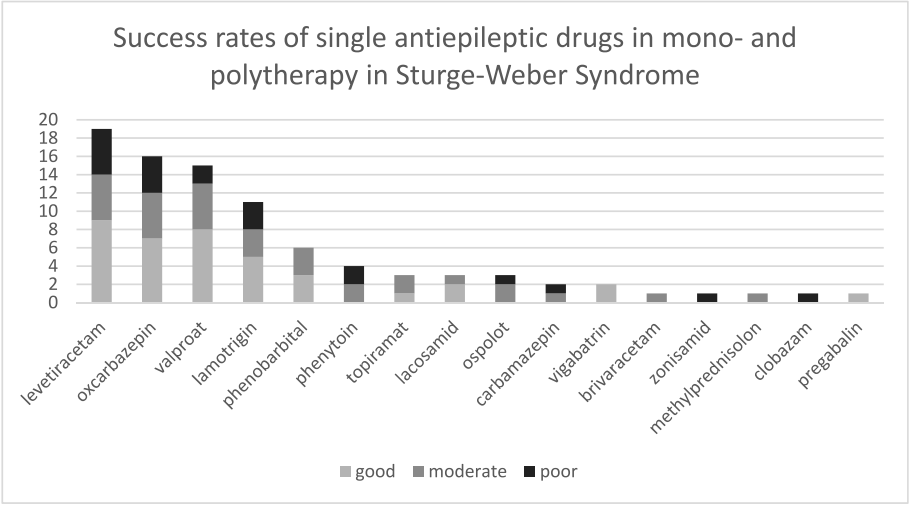

Fig. 5. Subjective estimation of success rates of substances, as rated by attending child neurologist for whole therapy combination; includes only current therapies.

pre-symptomatic cases suspicious for SWS [67]. As all patients from our purely pediatric cohort were reported to be diagnosed within the first two years of life, our data point towards a possible diagnostic improvement within the pediatric age group.

4.3. Diagnostic procedures

In the past few years, a paradigm shift in diagnostics has occurred. According to multidisciplinary U.S. consensus guidelines [67,68], sedated cerebral MRI is only necessary in young children (newborns, infants) suspicious for SWS after the first occurrence of seizures or if neurological abnormalities are present. Baseline neurologic and ophthalmologic evaluations as well as regular follow-ups are recommended in all children with a high-risk FPB [68]. These findings are reflected in our cohort, which included six patients diagnosed with SWS over four weeks up to 13 months before their first seizure, and four patients have remained seizure-free. In our cohort, *median age at diagnosis* was 5.0 months and one fourth of cases were diagnosed in the neonatal period. Thus, the proportion of neonatal diagnosis is in line with the U.S. SWS Registry data (33.6 %) [44]). Yet, our purely pediatric cohort indicates progress with regard to the timing of diagnosis when compared to the above-named registry data [44] as all children in our cohort were diagnosed within the first two years of life. *Median age at first seizure* was 6.5 months in our cohort, in line with past studies [62,

Table 3
(Online-only): Unless otherwise stated, median and interquartile range are given. Differences to 100 % are due to rounding errors and/or to missing values. † Multiple responses are possible for the category "cerebral involvement", resulting in a total sum> 100 %.

Patient characteristics	No treatment with aspirin (n = 23), %	Treatment with aspirin (n = 21), %	Comparison aspirin vs. no aspirin
Diagnostics			p = 0.29
- age at diagnosis [months], median and range	4 (0–24.0)	7 (0–21.0)	
Epilepsy/seizures			
- age at first seizure [months]	6 (0.75–15.0)	8 (0.67–20.0)	p = 0.905
- current seizure frequency			p = 0.80
- never had a seizure	3 (13.0)	1 (5.0)	
- >1 prior seizure, now seizure-free	8 (34.8)	9 (42.9)	
- breakthrough seizures	1 (4.3)	3 (14.3)	
- monthly seizures	1 (4.3)	2 (9.5)	
- weekly seizures or more	3 (13.0)	3 (14.3)	
- unknown/NA	5 (21.9)	3 (14.3)	
- types of seizures			
- focal	3 (13.0)	1 (5.0)	
- generalized	9 (39.1)	10 (47.6)	
- focal and generalized	7 (30.4)	6 (28.6)	
Antiseizure medication			
- number of ASM (median, IQR)	1 (1–2)	2 (1–2)	p = 0.18
Epilepsy surgery			
- surgery perfomed	4	0	
- type of surgery	1 hemispherectomy 1: hemispherotomy 2: cortical excision	(2 evaluated)	not eval.
Cerebral involvement †			
- cerebral atrophy	17 (73.9)	17 (81.0)	p = 0.42
- cerebral calcifications	5 (21.7)	12 (57.1)	**p = 0.032***
- stroke-like episodes	5 (21.7)	3 (14.3)	p = 0.701
Neurocognitive status/development			
- SWS neuroscore	7 (1.75–9.25)	6 (4.0–8.0)	p = 0.75
- cognitive impairment			p = 0.53
- none	7 (30.4)	8 (38.1)	
- mild	1 (4.3)	2 (9.5)	
- slight	1 (4.3)	1 (4.8)	
- moderate	6 (26.1)	1 (4.8)	
- severe	1 (4.3)	2 (9.5)	
- very severe	3 (13.0)	3 (14.3)	
- paresis**			p = 0.71
– 0: none	10 (0.43)	6 (28.6)	
– 1: mild, body posture affected	2 (8.7)	3 (14.3)	
– 2: only fine motricity	1 (4.3)	4 (19.0)	
– 3: significant, fine and gross motricity	6 (26.1)	4 (19.0)	
– 4: severe, fine and gross motricity	4 (17.4)	3 (14.3)	
Skin involvement			p = 0.76
- no FPB	3 (13.0)	3 (14.3)	
- unilateral FPB	13 (56.5))	9 (42.9)	
- bilateral FPB	6 (26.1)	7 (33.3)	

69,70]; whereas some studies (108 cases, 34 cases each) showed later average seizure onset [71,72], and one study (15 cases) showed an earlier seizure onset [73] i.e., 4.5 months. Our finding that 78 % of patients present with seizure onset within the first year of life is in line with the 75 % rate in a previous study [69].

4.4. Therapy and therapeutic success

Only few studies have investigated the ASM response in SWS patients. In our cohort, a wide range of different ASM was used, in line with a study considering 108 SWS patients with a history of ≥1 seizure and treatment with ≥1 ASM [71]. The most commonly used ASM in our cohort were OXC and LEV, in line with that past study [71]. Widely different combinations of ASM were used in our cohort (OXC + LEV; OXC + valproate), in line with that study [71] (OXC + LEV; OXC + topiramate). OXC/carbamazepine were the most frequently currently used ASM in monotherapy in seizure-free patients in the Kaplan cohort, and LEV was the most frequently currently used ASM in monotherapy in patients with uncontrolled seizures [71]. In our study, patients most commonly received ASM monotherapy with LEV, and monotherapy with either LEV or OXC were commonly associated with "good" treatment success. In the Kaplan cohort, LEV was associated with significantly more side effects than other substances. Side effects due to ASM were not investigated in our cohort. Kaplan et al. noted a trend towards increasing use of LEV in SWS patients – a finding compatible with the high rates in our study. In the to date largest and most recent cohort including 268 predominantly pediatric U.S. SWS patients, Smegal et al. [74] reported in 2021 that LEV, OXC and phenobarbital (in descending order) were the most frequently used ASMs – and thus their data show good accordance to data from our study. These U.S. data are strikingly similar to data from our European cohort regarding the number of ASM used per patient[4] and regarding the proportion of patients on aspirin (Smegal et al. 44.8 %; in our cohort 44.7 %). As seizure control is of paramount importance for the neurodevelopmental outcome of these patients and ASM treatment is usually long-term, the choice of effective ASM at the lowest adverse event rate is a central objective in SWS management. Aspirin therapy has long been a controversy in SWS, and some studies support its administration (i.e. [31,41,75]). In our cohort, we found numerical reductions in stroke-like episodes and in severe/-significant hemiparesis, but the finding did not reach statistical significance. Seizure frequency and overall outcome were comparable. However, causal interpretation of these findings is not possible due to our cross-sectional study design. Thus, this important subject warrants further investigation in larger, longitudinal cohort studies. As also shown in our cohort, epilepsy surgery is another promising therapy option for selected SWS patients. In a cohort of 52 pediatric patients with refractory epilepsy which included 42 % patients with congenital lesions, Ramantani et al. [76] demonstrated high rates of seizure freedom (83 %), irrespective of epilepsy etiology. Furthermore, the authors showed that epilepsy surgery is not necessarily restricted to unilateral lesions. Therapy success following hemispherotomy was re-assessed in a large European cohort with 457 children including 36 patients with SWS [40]. This study identified previous surgical interventions, contralateral MRI findings and left hemispherotomy as risk factors for poor seizure control. Notably, 27 SWS patients (75 % of that cohort) achieved seizure freedom through surgery [40].

4.5. Strengths and limitations of the study

Our study provides detailed clinical data from a multinational European pediatric cohort of SWS patients. The data were acquired by a well-established child neurologist network and all diagnoses were ascertained by experienced child neurologists. We present detailed comprehensive data, as provided by both patients' caregivers and neuropaediatricians. Our analyses include prevalence rates and corresponding confidence intervals for Germany, Switzerland and Austria, and they give insight into key areas for SWS research, including

[4] Smegal et al. 0 ASM = 10.4 %, 1 ASM = 37.7 %, 2 ASM = 34.0 %, 3 ASM = 14.2 %, 4 ASM or more = 3.7 %; vs. our cohort: 0 ASM = 12.8 %, 1 ASM = 31.9 %, 2 ASM = 36.2 %, 3 ASM = 14.9 %, 4 ASM = 2.1 %.

presymptomatic diagnosis and treatment. The main limitation of our study is our use of paper questionnaires, resulting in time-consuming data collection and data entry. Additionally, we acknowledge that reporting bias may have resulted in incomplete registration as ESNEK is a non-obligatory network.

5. Conclusions

In this first population-based European pediatric SWS cohort, the condition was commonly diagnosed within the first year of life. 40 % of the cohort were seizure-free at inclusion; only 8.5 % of the cohort underwent epilepsy surgery. The majority of patients required ASM for seizure control. The comparison of our cohort to published data from U. S. registries and case series showed good overall concordance. While our results indicate diagnostic improvement compared to data from previous published studies, epilepsy management in SWS remains a challenge.

Authors' contributions

Study idea: SD. Study design: SD, SM. Data acquisition: HK, AB, GCK, GR, BW, MP, RT, KB, SS. Coordination of child neurologists' network for data acquisition: SS, KB. Statistical analysis: SD. Drafting of manuscript: SD. Critical revision of the manuscript: all authors. Study supervision: SM.

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Declaration of competing interest

Interim results of this study were presented at a Meeting of the German National Sturge-Weber Foundation (IG, "Interessensgemeinschaft" SWS) in Herbstein/Germany in 2019. The main study findings were presented at the German Pediatric National conference as a poster in 2020.

All authors confirm that they have no conflicting interests.

Appendix

- Questionnaires for families
- Questionnaires for child neurologists

References

[1] # 185300, STURGE-WEBER SYNDROME; SWS [Internet]. [cited 2021, June 27th]. Available from: https://www.omim.org/entry/185300.
[2] W.A. Sturge, A case of partial epilepsy, apparently due to a lesion of one of the vasomotor centres of the brain, Trans Clin Soc Lond. 12 (1879) 162–167.
[3] F.P. Weber, Right-sided hemi-hypotrophy resulting from right-sided congenital spastic hemiplegia, with a morbid condition of the left side of the brain, revealed by radiograms, J. Neurol. Psychopathol. 3 (10) (1922) 134–139.
[4] J.M. Pearce, Sturge-Weber syndrome (encephalotrigeminal or leptomeningeal angiomatosis), J. Neurol. Neurosurg. Psychiatry 77 (11) (2006) 1291–1292.
[5] M.D. Shirley, H. Tang, C.J. Gallione, J.D. Baugher, L.P. Frelin, B. Cohen, et al., Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ, N. Engl. J. Med. 368 (21) (2013) 1971–1979.
[6] R. Fjaer, K. Marciniak, O. Sundnes, H. Hjorthaug, Y. Sheng, C. Hammarstrom, et al., A novel somatic mutation in GNB2 provides new insights to the pathogenesis of Sturge-weber syndrome, Hum. Mol. Genet. (2021).
[7] A.F. Luat, C. Juhasz, J.A. Loeb, H.T. Chugani, S.J. Falchek, B. Jain, et al., Neurological Complications of sturge-weber syndrome: current status and unmet needs, Pediatr. Neurol. 98 (2019) 31–38.
[8] A.M. Comi, Update on Sturge-Weber syndrome: diagnosis, treatment, quantitative measures, and controversies, Lymphatic Res. Biol. 5 (4) (2007) 257–264.
[9] A.M. Comi, Sturge-Weber syndrome, Handb. Clin. Neurol. 132 (2015) 157–168.
[10] M. Jimenez-Legido, A. Martinez-de-Azagra-Garde, B. Bernardino-Cuesta, I. Solis-Muniz, V. Soto-Insuga, V. Cantarin-Extremera, et al., Utility of the transcranial Doppler in the evaluation and follow-up of children with Sturge-Weber Syndrome, Eur. J. Paediatr. Neurol. 27 (2020) 60–66.
[11] L.C. Jordan, R.J. Wityk, M.M. Dowling, M.R. DeJong, A.M. Comi, Transcranial Doppler ultrasound in children with Sturge-Weber syndrome, J. Child Neurol. 23 (2) (2008) 137–143.
[12] J. Reesman, R. Gray, S.J. Suskauer, L.M. Ferenc, E.H. Kossoff, D.D. Lin, et al., Hemiparesis is a clinical correlate of general adaptive dysfunction in children and adolescents with Sturge-Weber syndrome, J. Child Neurol. 24 (6) (2009) 701–708.
[13] J. Wu, B. Tarabishy, J. Hu, Y. Miao, Z. Cai, Y. Xuan, et al., Cortical calcification in Sturge-Weber Syndrome on MRI-SWI: relation to brain perfusion status and seizure severity, J. Magn. Reson. Imag. 34 (4) (2011) 791–798.
[14] J.W. Jeong, H.T. Chugani, M.E. Behen, W. Guy, C. Juhasz, Quantitative assessment of brain networks in children with sturge-weber syndrome using resting state functional magnetic resonance imaging (MRI), J. Child Neurol. 28 (11) (2013) 1448–1455.
[15] J.W. Jeong, H.T. Chugani, C. Juhasz, Localization of function-specific segments of the primary motor pathway in children with Sturge-Weber syndrome: a multimodal imaging analysis, J. Magn. Reson. Imag. 38 (5) (2013) 1152–1161.
[16] E.I. Lance, K.E. Lanier, T.A. Zabel, A.M. Comi, Stimulant use in patients with sturge-weber syndrome: safety and efficacy, Pediatr. Neurol. 51 (5) (2014) 675–680.
[17] Z. Pfund, K. Kagawa, C. Juhasz, C. Shen, J.S. Lee, D.C. Chugani, et al., Quantitative analysis of gray- and white-matter volumes and glucose metabolism in Sturge-Weber syndrome, J. Child Neurol. 18 (2) (2003) 119–126.
[18] T.M. Kelley, L.A. Hatfield, D.D. Lin, A.M. Comi, Quantitative analysis of cerebral cortical atrophy and correlation with clinical severity in unilateral Sturge-Weber syndrome, J. Child Neurol. 20 (11) (2005) 867–870.
[19] R.S. Miller, K.L. Ball, A.M. Comi, E.L. Germain-Lee, Growth hormone deficiency in Sturge-Weber syndrome, Arch. Dis. Child. 91 (4) (2006) 340–341.
[20] C. Juhasz, E.M. Haacke, J. Hu, Y. Xuan, M. Makki, M.E. Behen, et al., Multimodality imaging of cortical and white matter abnormalities in Sturge-Weber syndrome, AJNR Am J Neuroradiol 28 (5) (2007) 900–906.
[21] C.E. Batista, H.T. Chugani, J. Hu, E.M. Haacke, M.E. Behen, E.J. Helder, et al., Magnetic resonance spectroscopic imaging detects abnormalities in normal-appearing frontal lobe of patients with Sturge-Weber syndrome, J. Neuroimaging 18 (3) (2008) 306–313.
[22] E.H. Kossoff, J.L. Borsage, A.M. Comi, A pilot study of the modified Atkins diet for Sturge-Weber syndrome, Epilepsy Res. 92 (2–3) (2010) 240–243.
[23] B. Alkonyi, H.T. Chugani, S. Karia, M.E. Behen, C. Juhasz, Clinical outcomes in bilateral Sturge-Weber syndrome, Pediatr. Neurol. 44 (6) (2011) 443–449.
[24] B. Alkonyi, R.M. Govindan, H.T. Chugani, M.E. Behen, J.W. Jeong, C. Juhasz, Focal white matter abnormalities related to neurocognitive dysfunction: an objective diffusion tensor imaging study of children with Sturge-Weber syndrome, Pediatr. Res. 69 (1) (2011) 74–79.
[25] E.H. Kaplan, E.A. Offermann, J.W. Sievers, A.M. Comi, Cannabidiol treatment for refractory seizures in sturge-weber syndrome, Pediatr. Neurol. 71 (2017) 18–23.
[26] E.A. Offermann, A. Sreenivasan, M.R. DeJong, D.D.M. Lin, C.E. McCulloch, M. G. Chung, et al., Reliability and clinical correlation of transcranial Doppler ultrasound in sturge-weber syndrome, Pediatr. Neurol. 74 (2017) 15–23.
[27] S.K. Sundaram, S.K. Michelhaugh, N.V. Klinger, W.J. Kupsky, S. Sood, H. T. Chugani, et al., GNAQ mutation in the venous vascular malformation and underlying brain tissue in sturge-weber syndrome, Neuropediatrics 48 (5) (2017) 385–389.
[28] F. Gallop, T. Fosi, P. Prabhakar, S.E. Aylett, Flunarizine for headache prophylaxis in children with sturge-weber syndrome, Pediatr. Neurol. 93 (2019) 27–33.
[29] L. Chapieski, A. Friedman, D. Lachar, Psychological functioning in children and adolescents with Sturge-Weber syndrome, J. Child Neurol. 15 (10) (2000) 660–665.
[30] M.E. Behen, C. Juhasz, C. Wolfe-Christensen, W. Guy, S. Halverson, R. Rothermel, et al., Brain damage and IQ in unilateral Sturge-Weber syndrome: support for a "fresh start" hypothesis, Epilepsy Behav. 22 (2) (2011) 352–357.
[31] E.I. Lance, A.K. Sreenivasan, T.A. Zabel, E.H. Kossoff, A.M. Comi, Aspirin use in Sturge-Weber syndrome: side effects and clinical outcomes, J. Child Neurol. 28 (2) (2013) 213–218.
[32] E.H. Kossoff, L.A. Hatfield, K.L. Ball, A.M. Comi, Comorbidity of epilepsy and headache in patients with Sturge-Weber syndrome, J. Child Neurol. 20 (8) (2005) 678–682.
[33] E.H. Kossoff, C. Buck, J.M. Freeman, Outcomes of 32 hemispherectomies for Sturge-Weber syndrome worldwide, Neurology 59 (11) (2002) 1735–1738.
[34] B. Alkonyi, H.T. Chugani, C. Juhasz, Transient focal cortical increase of interictal glucose metabolism in Sturge-Weber syndrome: implications for epileptogenesis, Epilepsia 52 (7) (2011) 1265–1272.
[35] V.K. Pilli, M.E. Behen, J. Hu, Y. Xuan, J. Janisse, H.T. Chugani, et al., Clinical and metabolic correlates of cerebral calcifications in Sturge-Weber syndrome, Dev. Med. Child Neurol. 59 (9) (2017) 952–958.
[36] E.H. Kossoff, C.D. Bachur, A.M. Quain, J.B. Ewen, A.M. Comi, EEG evolution in Sturge-Weber syndrome, Epilepsy Res. 108 (4) (2014) 816–819.
[37] L. Arkush, P. Prabhakar, R.C. Scott, S.E. Aylett, Headache in children with Sturge-Weber syndrome - prevalence, associations and impact, Eur. J. Paediatr. Neurol. 27 (2020) 43–48.
[38] R.P. Tillmann, K. Ray, S.E. Aylett, Transient episodes of hemiparesis in sturge weber syndrome - causes, incidence and recovery, Eur. J. Paediatr. Neurol. 25 (2020) 90–96.

[39] A.M. Day, C.E. McCulloch, A.M. Hammill, C. Juhasz, W.D. Lo, A.L. Pinto, et al., Physical and family history variables associated with neurological and cognitive development in sturge-weber syndrome, Pediatr. Neurol. 96 (2019) 30–36.
[40] G. Ramantani, C. Bulteau, D. Cserpan, W.M. Otte, G. Dorfmuller, J.H. Cross, et al., Not surgical technique, but etiology, contralateral MRI, prior surgery, and side of surgery determine seizure outcome after pediatric hemispherotomy, Epilepsia 64 (5) (2023) 1214–1224.
[41] M.J. Bay, E.H. Kossoff, C.U. Lehmann, T.A. Zabel, A.M. Comi, Survey of aspirin use in Sturge-Weber syndrome, J. Child Neurol. 26 (6) (2011) 692–702.
[42] S. Jagtap, G. Srinivas, K.J. Harsha, N. Radhakrishnan, A. Radhakrishnan, Sturge-Weber syndrome: clinical spectrum, disease course, and outcome of 30 patients, J. Child Neurol. 28 (6) (2013) 725–731.
[43] M. Dymerska, A.Y. Kirkorian, E.A. Offermann, D.D. Lin, A.M. Comi, B.A. Cohen, Size of facial port-wine birthmark may predict neurologic outcome in sturge-weber syndrome, J. Pediatr. 188 (2017) 205–209.
[44] S. Cho, B. Maharathi, K.L. Ball, J.A. Loeb, J. Pevsner, Sturge-Weber syndrome patient registry: delayed diagnosis and poor seizure control, J. Pediatr. 215 (2019) 158–163.
[45] K. Brockmann, Erhebung Seltener Neurologischer Erkrankungen im Kindesalter, Neuropediatrics (2014).
[46] S.C. Disse, S.P. Toelle, S. Schroeder, M. Theiler, L. Weibel, P. Broser, et al., Epidemiology, clinical features, and use of early supportive measures in PHACE syndrome: a European multinational observational study, Neuroepidemiology 54 (5) (2020) 383–391.
[47] E.S. Roach, Neurocutaneous syndromes, Pediatr. Clin. 39 (4) (1992) 591–620.
[48] B. Kavanaugh, A. Sreenivasan, C. Bachur, A. Papazoglou, A. Comi, T.A. Zabel, [Formula: see text]Intellectual and adaptive functioning in Sturge-Weber Syndrome, Child Neuropsychol. : a journal on normal and abnormal development in childhood and adolescence 22 (6) (2016) 635–648.
[49] RStudio. version 1.2.1335 ed2017, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2017. URL: https://www.R-project.org.
[50] Ständige Wohnbevölkerung nach Alter, Kanton, Bezirk und Gemeinde, 2010-2017, Bundesamt für Statistik, Schweizerische Eidgenossenschaft, 2018 [cited 2019, August 25th].
[51] Ständige Wohnbevölkerung in der Schweiz nach Alter und Geschlecht am 31. Dezember 2018 [Internet]. 2019 [cited 2019, March 31st]. Available from: https://de.statista.com/statistik/daten/studie/412104/umfrage/bevoelkerung-in-der-schweiz-nach-altersgruppen-und-geschlecht/.
[52] Bevölkerung - Zahl der Einwohner in Deutschland nach Altersgruppen am 31. Dezember 2017 (in Millionen) (2019) [cited 2019, March 31st]. Available from: https://de.statista.com/statistik/daten/studie/1365/umfrage/bevoelkerung-deutschlands-nach-altersgruppen/.
[53] Bevölkerung: Deutschland, Stichtag, Altersjahre, Statistisches Bundesamt (Destatis), 2019 [cited 2019, August 25th]. Available from:.
[54] Zeit, Wohnbevölkerung im Jahresdurchschnitt und Alter in 15-Jahresgruppen nach Geschlecht (2019). https://statcube.at/statistik.at/ext/statcube/jsf/tableView/tableView.xhtml.
[55] W.D. Flanders, D.G. Kleinbaum, Basic models for disease occurrence in epidemiology, Int. J. Epidemiol. 24 (1) (1995) 1–7.
[56] R. Waelchli, S.E. Aylett, K. Robinson, W.K. Chong, A.E. Martinez, V.A. Kinsler, New vascular classification of port-wine stains: improving prediction of Sturge-Weber risk, Br. J. Dermatol. 171 (4) (2014) 861–867.
[57] H.T. Rihani, L.A. Dalvin, D.O. Hodge, J.S. Pulido, Incidence of Sturge-Weber syndrome and associated ocular involvement in Olmsted County, Minnesota, United States, Ophthalmic Genet. 41 (2) (2020) 108–124.
[58] C.A. Mason, R.S. Kirby, L.E. Sever, P.H. Langlois, Prevalence is the preferred measure of frequency of birth defects, Birth Defects Res A Clin Mol Teratol 73 (10) (2005) 690–692.
[59] Orphanet, Orphanet-The portal for rare diseases and orphan drugs (2020) [Available from: https://www.orpha.net/consor/cgi-bin/Education_AboutOrphanet.php?lng=EN.
[60] Procedural document on Epidemiology of rare disease in Orphanet (Prevalence, incidence and number of published cases or families)2019 July 27th (2021). Available from: https://www.orpha.net/orphacom/cahiers/docs/GB/Epidemiology_in_Orphanet_R1_Ann_Epi_EP_05.pdf.
[61] R. Nabbout, C. Juhasz, Sturge-Weber syndrome, Handb. Clin. Neurol. 111 (2013) 315–321.
[62] Orphanet, The portal for rare diseases and orphan drugs, Sturge-Weber syndrome Orphanet Encyclopaedia (2021) [Internet]. 2021 2022, July 18th. Available from: https://www.orpha.net/consor/www/cgi-bin/OC_Exp.php?lng=EN&Expert=3205.
[63] Prevalence of rare diseases: Bibliographic data, Orphanet Report Series, Rare Diseases collection, January 2022. Number 1 : Diseases listed in alphabetical order 2022 [Available from: https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf.
[64] A. Jakob, J. Whelan, M. Kordecki, R. Berner, B. Stiller, R. Arnold, et al., Kawasaki disease in Germany: a prospective, population-based study adjusted for underreporting, Pediatr. Infect. Dis. J. 35 (2) (2016) 129–134.
[65] J. Rosenbauer, P. Herzig, R. von Kries, A. Neu, G. Giani, Temporal, seasonal, and geographical incidence patterns of type I diabetes mellitus in children under 5 years of age in Germany, Diabetologia 42 (9) (1999) 1055–1059.
[66] K. Thomas-Sohl, A. Comi, Sturge weber syndrome, Atlas Genet Cytogenet Oncol Haematol 8 (4) (2004) 340–342.
[67] A.J. De la Torre, A.F. Luat, C. Juhasz, M.L. Ho, D.P. Argersinger, K.M. Cavuoto, et al., A multidisciplinary consensus for clinical care and research needs for sturge-weber syndrome, Pediatr. Neurol. 84 (2018) 11–20.
[68] S. Sabeti, K.L. Ball, S.K. Bhattacharya, E. Bitrian, L.S. Blieden, J.D. Brandt, et al., Consensus statement for the management and treatment of sturge-weber syndrome: neurology, neuroimaging, and ophthalmology recommendations, Pediatr. Neurol. 121 (2021) 59–66.
[69] E. Sujansky, S. Conradi, Sturge-Weber syndrome: age of onset of seizures and glaucoma and the prognosis for affected children, J. Child Neurol. 10 (1) (1995) 49–58.
[70] E. Sujansky, S. Conradi, Outcome of Sturge-Weber syndrome in 52 adults, Am. J. Med. Genet. 57 (1) (1995) 35–45.
[71] E.H. Kaplan, E.H. Kossoff, C.D. Bachur, M. Gholston, J. Hahn, M. Widlus, et al., Anticonvulsant efficacy in sturge-weber syndrome, Pediatr. Neurol. 58 (2016) 31–36.
[72] A.F. Luat, M.E. Behen, H.T. Chugani, C. Juhasz, Cognitive and motor outcomes in children with unilateral Sturge-Weber syndrome: effect of age at seizure onset and side of brain involvement, Epilepsy Behav. 80 (2018) 202–207.
[73] M. Piram, G. Lorette, D. Sirinelli, D. Herbreteau, B. Giraudeau, A. Maruani, Sturge-Weber syndrome in patients with facial port-wine stain, Pediatr. Dermatol. 29 (1) (2012) 32–37.
[74] L.F. Smegal, A.J. Sebold, A.M. Hammill, C. Juhasz, W.D. Lo, D.K. Miles, et al., Multicenter research data of epilepsy management in patients with sturge-weber syndrome, Pediatr. Neurol. 119 (2021) 3–10.
[75] A.M. Day, A.M. Hammill, C. Juhasz, A.L. Pinto, E.S. Roach, C.E. McCulloch, et al., Hypothesis: presymptomatic treatment of sturge-weber syndrome with aspirin and antiepileptic drugs may delay seizure onset, Pediatr. Neurol. 90 (2019) 8–12.
[76] G. Ramantani, N.E. Kadish, A. Brandt, K. Strobl, A. Stathi, G. Wiegand, et al., Seizure control and developmental trajectories after hemispherotomy for refractory epilepsy in childhood and adolescence, Epilepsia 54 (6) (2013) 1046–1055.