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ORIGINAL COMMUNICATION

A review of the natural history of Sturge–Weber syndrome through adulthood

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Abstract

Background Sturge–Weber syndrome (SWS) is a neurocutaneous disorder caused by a somatic mutation in the *GNAQ* gene, leading to capillary venous malformations with neurological, ocular, and cutaneous abnormalities. Descriptions of adult and elderly patients with SWS are scarce compared to those of neonates or children.

Methods We reviewed clinical, neuro-radiological and electroencephalographical findings of adult patients diagnosed with SWS, treated in our tertiary center for rare epilepsies.

Results Ten adult patients were identified with a median age of 48 years at inclusion. All patients had seizures, with features of temporal lobe involvement for five patients. One patient presented typical drug-resistant mesial temporal seizures with ipsilateral hippocampal sclerosis and leptomeningeal enhancement, and was treated surgically. Other patients presented typical neurological and brain imaging features found in SWS. One patient without visible leptomeningeal angioma or brain calcifications presented neurological symptoms (tonic–clonic generalized seizures) for the first time at the age of 56. Two of the oldest patients in our cohort with supratentorial leptomeningeal angioma displayed contralateral cerebellar atrophy, consistent with crossed cerebellar diaschisis. Over 70 years of follow-up data were available for one patient whose epilepsy started at the age of 6 months, offering a vast overview of the course of SWS, in particular the onset of dementia and contralateral micro-bleeds in relation to the leptomeningeal angioma.

Conclusion The long follow-up of our cohort allows for a description of the course of SWS and a characterization of uncommon neurological features in adult and elderly patients.

Keywords Sturge–Weber syndrome · Leptomeningeal angioma · Epilepsy · GNAQ · MRI · EEG

Introduction

Sturge–Weber syndrome (SWS) is a rare congenital disorder characterized by cutaneous, neurological, and ocular manifestations, due to capillary venous malformations in skin, brain, and eye, caused by a somatic mutation (p.Arg183Gln, p.R183Q) in the guanine nucleotide-binding protein G(q) subunit alpha (*GNAQ*) gene [1, 2]. In addition to facial angioma, SWS includes ocular manifestations, in particular glaucoma, and the development of a leptomeningeal angioma leading to chronic brain injury [3].

Neurological manifestations include various acute and chronic disorders [4]. Epilepsy is the most frequent neurological manifestation of SWS, found in almost all patients [5]. Seizures occur during the first year of life in 75% of patients [6]. Adult onset of epilepsy is very rare [7–13]. Headaches also begin in childhood, with a median age of 8 years [14]. Stroke-like (SL) episodes are reported in children with SWS but less frequently in adult patients [15]. Focal neurological deficits develop gradually over the course of the disorder and may worsen following seizures and SL episodes [16]. The first signs of intellectual disability usually

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appear during childhood [5]. This disability is severe in a third of children and young adult patients. An intellectual disability is reported in 55% of adult patients [16, 17].

Contrast-enhanced brain MRI is the gold standard for diagnosis of leptomeningeal angioma. Leptomeningeal angioma is unilateral in most patients, with ipsilateral facial angioma and ocular abnormalities. Brain imaging can also show variable features, such as ipsilateral calcifications, cerebral atrophy, and dilated choroid plexus [1]. EEG can be normal or show asymmetrical background activity amplitude or frequency as well as interictal activities or seizures [17].

The diagnosis of SWS is usually made by pediatricians for whom SWS is a well-known disorder as most studies report neonates and children. Data on adult patients are scarce and most studies are based on self-assessment questionnaires or telephone studies with no, or at best a short, follow-up. The goal of our study is to describe the general and neurological clinical features of SWS adult patients, as well as neuro-radiological and electroencephalographical features.

Methods

We reviewed medical records, EEG, and brain imaging of adult patients with a diagnosis of SWS in the Epilepsy Unit and Reference Center for Rare Epilepsies at Pitié-Salpêtrière Hospital (Paris, France) from 1987 to 2018. Records were reviewed by GV and VN. This study was conducted according to the French legislation and authorized by the CNIL (the French data protection authority, No. 2211991). Patients were informed about that their anonymized data would be used in this study. Anonymized data not published within this article will be made available by request from any qualified investigator.

Clinical data

General clinical characteristics were collected: sex, age at inclusion, ethnic origin, personal and familial medical history, personal history of febrile seizure, head trauma or meningoencephalitis, age at SWS diagnosis, circumstances of SWS diagnosis (screening without neurological events or diagnosis after first neurological manifestation), gynecological history for women, and social history.

Neurological features included i) epilepsy: age at first seizure, types and semiology of seizures, psychogenic non-epileptic seizures (PNES), status epilepticus (SE), postictal symptoms, highest seizure frequency, longest seizure-free period, history and side effects of antiepileptic drugs (AED), drug-resistant epilepsy [18], epilepsy surgery and post-operative evolution [19], use of vagus nerve stimulation, use of specific diets; ii) headaches; iii) motor, sensory and/or visual deficits; iv) neurodevelopmental and cognitive symptoms; v) psychiatric and behavior disorders; vi) SL episodes.

Dermatological and ophthalmologic features were also collected.

Neuro-radiological data

We reviewed all brain imaging exams: (i) CT-scans: parenchymal and bone sequences with (if available) and without contrast; (ii) MRI: T1-weighted images, with (if available) and without contrast, T2-weighted and T2-FLAIR images, diffusion-weighted imaging (DWI), magnetic susceptibility images (T2 gradient echo (GE) and/or susceptibility-weighted angiography (SWAN) sequences) and intracranial proximal arteries on time of flight (TOF) sequences.

The following data were assessed: leptomeningeal enhancement, calcifications, cerebral atrophy, postictal abnormalities, dilated choroid plexus, white matter abnormalities, deep venous dilatation, hippocampal abnormalities, frontal sinus pneumatization, dural enhancement, intracranial proximal vessels abnormalities, developmental venous anomalies, infratentorial abnormalities, and radiological evolution.

Electroencephalographical data

Digital EEG were recorded using Brainnet Medatec^{R} or SystemPLUS EVOLUTION Micromed^{R} systems, with 8–21 electrodes (10–20 international system placement). Duration of EEG was 20 or 90 min. One patient benefited from continuous video-EEG, prolonged for up to 10 days, with 27 electrodes. EEG included repetitive stimulations: eye-openings, auditive and sensory stimulations, 3 min hyperventilation (HPV) and 1–50 Hz intermittent photic stimulation (IPS).

The following data were analyzed: background activity (frequency, amplitude, and reactivity to eye-opening and auditive and sensory stimulations), changes due to HPV and IPS, sleep, interictal activities and seizures.

Results

Clinical findings

General features (Table 1)

Ten adult patients, three men and seven women, were included. Median age at inclusion was 48 years (range 21–74). Median age at SWS diagnosis was 19 years (range 0.5–60). In all patients, diagnosis was made after the onset

Table 1 General features

No.	Gender	Age at inclusion (years)	Age at SWS diagnosis (years)	Ethnic origin
p1	F	21	19	Caucasian
p2	F	53	46	Asian
p3	M	71	60	African
p4	F	74	51	Hispanic
p5	F	70	8	Caucasian
p6	F	32	8	Middle East
p7	F	71	0.5	Caucasian
p8	M	43	31	African
p9	M	39	NA	Middle East
p10	F	27	2.5	Hispanic

F female, *M* male, *NA* not available, *SWS* Sturge–Weber syndrome.

of neurological manifestations. Median duration of follow-up was 23 years (range 2–70.5).

Social and occupational categories varied between patients. Five patients (p3, p6, p8, p9 and p10) were employed, one patient (p1) was enrolled in business school, two patients (p2 and p5) had interrupted their education, one patient (p7) had worked until retirement, and one patient (p4) had stopped working due to disability.

Three patients (p2, p4 and p6) had successful past pregnancies without complications.

Dermatological and ophthalmologic features are summarized in Table 2.

One patient (p7) died at the age of 71 years.

Neurological features (Table 3)

Epilepsy was the first neurological manifestation of SWS in nine out of ten patients. Median age at first seizure was 7 years (range 0.5–56). Epilepsy began during childhood for seven patients and during adulthood for three. Patients presented focal seizures (FS), sometimes with bilateral tonic–clonic evolution, or generalized tonic–clonic seizures (GTCS). Seizure semiology was suggestive of occipital ($n=3$) and parietal ($n=3$) lobe involvement. Ictal visual symptoms were only reported by one patient. Five patients displayed seizures with temporal lobe features.

The median seizure frequency was 1 seizure a week (range twice a year–twice a day). The median seizure-free period was 3.5 years (range 0.25–16). Four patients had SE during the course of the disorder, and SE was the first epileptic manifestation for two of these patients. Postictal symptoms were prolonged in three patients who presented hemiparesis or hemiplegia for a few days up to two weeks. None of the patients presented PNES.

All patients received AED after epilepsy onset and none as preventive therapy before seizures. Seven patients had drug-resistant epilepsy according to ILAE criteria. At inclusion, patients were treated with a mean of three AED (range 1–6). None of AED seemed to be more effective than the others. Side effects of AED were similar to those usually

Table 2 Main dermatological and ophthalmologic features

No.	Dermatological features	Ophthalmologic features
p1	Right V1 facial angioma Laser treatment in childhood before seizures and SWS diagnosis	
p2	Right V1 and left V1–V2 facial angioma with gingival hypertrophy Naevus of Ota	
p3	Right V1–V2–V3 hypertrophic facial angioma with buccal extension	Right glaucoma Right choroidal angioma Right retinal detachment Right episcleral vessel dilatation Bilateral cataract
p4	Right V2 facial angioma	Bilateral cataract
p5	Left V1 facial angioma	Left glaucoma Left episcleral vessel dilatation
p6	Right V1 facial angioma Laser treatment in adulthood after SWS diagnosis	
p7	Right V1 facial angioma	Bilateral cataract
p8	Left V1 facial angioma	Left glaucoma
p9	Right V1 facial angioma	Right choroidal angioma Right episcleral vessels angioma
p10	Right V1 facial angioma	

SWS Sturge–Weber syndrome, *V1* ophthalmic branch of trigeminal nerve, *V2* maxillary branch of trigeminal nerve, *V3* mandibular branch of trigeminal nerve

Table 3 Neurological features

No.	Age at first seizure/SE (years)	Seizure semiology (except SE)	Status epilepticus	Postictal symptoms	AED at last visit	Headaches	Focal deficits	Neurodevelopmental and cognitive symptoms	Psychiatric and behavioral disorders	Stroke-like episodes
p1	19	Headache, chest tightness and nausea then tonic posture or foreign limb sensation of left UL ± bilateral tonic–clonic seizure	Generalized convulsive SE (at 19 years) revealing EBV meningoencephalitis	Confusion and left hemiplegia for a few days	LEV	Migraine (since 18 years), sometimes preceding seizures or SL NSAID effective		Mild apraxia and dysexecutive symptoms	Attentional disorders and irritability	Left hemiplegia (since adulthood)
p2	17	(1) Left-sided oculocephalic deviation then impaired awareness (2) Generalized tonic–clonic seizure	Generalized convulsive SE (at 46 years)	Transient confusion	LEV		Left hemiparesis (since 30 years)			
p3	56	Generalized tonic–clonic seizure		Transient headache	CLB, LEV, VPA					
p4	8	(1) Rotatory vertigo then bilateral tonic–clonic seizure (2) Impaired awareness with verbal and gesture automatisms then bilateral tonic–clonic seizure (3) Generalized tonic–clonic seizures			CLB, ESL, LCS		Left IHQ	Major memory disorders and dysexecutive symptoms	Irritability, depressive and psychotic disorders, insomnia	
p5	8	(1) Impaired awareness with oro-alimentary and gesture automatisms (2) Generalized tonic–clonic seizure			CBZ, CLB, PB	Migraine Aspirin and ergotamine effective TPM ineffective		Language disorders		
p6	1.25	(1) Left-sided visual hallucinations then bilateral tonic–clonic seizure (2) Generalized tonic–clonic seizure		Transient left HH and headache	LEV	Postictal non-migrainous headaches (since age 22 years) NSAID effective			Attentional and depressive disorders, insomnia	

Table 3 (continued)

No.	Age at first seizure/SE (years)	Seizure semiology (except SE)	Status epilepticus	Postictal symptoms	AED at last visit	Headaches	Focal deficits	Neurodevelopmental and cognitive symptoms	Psychiatric and behavioral disorders	Stroke-like episodes
p7	0.5	(1) Tonic posture ± tonic–clonic movements of left-sided HC then bilateral tonic–clonic seizure (2) Generalized tonic–clonic seizure	Generalized convulsive SE (at 4 and 68 years)	Left hemiplegia for 10–15 days	CBZ, CLB, LCS, LEV, PB, VPA	Migraine preceding SL TPM ineffective	Left hemiparesis (since 4.5 years) evolving toward left hemiplegia in adulthood associated with left anesthesia and HH	Dementia		Left hemiplegia (since adulthood)
p8	2.5	(1) Cold feeling then déja-vu and childhood memories reminiscence then impaired awareness with verbal automatisms (Cameroon language) and right UL dystonia ± bilateral tonic–clonic seizure (2) Generalized tonic–clonic seizure			PB, ZNS			Memory disorders		
p9	3	(1) Impaired awareness with tonic posture of left UL (2) Rotatory vertigo and fear feeling then oro-alimentary and motor right hand automatisms and left UL dystonia ± bilateral tonic–clonic seizure (3) Generalized tonic–clonic seizure		Left hemiparesis for a few days	CBZ, CNZ, LEV, PRM		Left IHQ		Anxiety, depressive and psychotic disorders, insomnia	
p10	6	Generalized tonic–clonic seizure	Left hemiclonic SE (since 6 years)		CBZ, STP			Delayed language development and reading difficulties		Left hemiplegia (since 2.5 years)

AED antiepileptic drugs, *CBZ* carbamazepine, *CLB* clobazam, *CNZ* clonazepam, *EBV* Epstein-Barr virus, *ESL* eslicarbazepine, *HC* hemicorpus, *HH* homonymous hemianopsia, *IHQ* inferior homonymous quadranopsia, *LCS* lacosamide, *LEV* levetiracetam, *NSAID* non-steroidal anti-inflammatory drugs, *PB* phenobarbital, *PRM* primidone, *SE* status epilepticus, *SL* stroke-like, *STP* stiripentol, *TPM* topiramate, *UL* upper limb, *VPA* valproate, *ZNS* zonisamide

reported. None of patients had vagus nerve stimulation nor used specific diets.

One patient (p8) had surgery for left hippocampal sclerosis (HS). This patient showed GTCS starting at the age of 2.5 years with no history of febrile seizures or SE. As an adolescent, he began presenting FS suggestive of mesial temporal lobe epilepsy. Ten days of continuous video-EEG monitoring recorded left temporal interictal activities and seizures concordant with left HS on MRI. Left selective amygdalo-hippocampectomy was performed at age 38. Histopathological analysis showed neuronal loss in Ammon's horn with reactional gliosis and no subiculum lesions, compatible with ILAE type 1 HS [20]. Vascular density and leptomeningeal spaces were normal. He was seizure-free at last follow-up, 2 years after surgery (class 1 ILAE).

Four patients had headaches, beginning in adulthood for two (data not available for the two others). Three of these patients presented migraines, and migraines preceded SL episodes in two patients.

Two patients presented a permanent motor deficit which appeared in childhood for one and adulthood for the other. The motor deficit worsened over time and both patients were wheelchair-bound. Visual field abnormalities were found in three patients. One patient displayed left upper limb cerebellar syndrome.

One patient had delayed language development and reading difficulties and five others displayed cognitive symptoms, with one patient diagnosed with dementia.

Psychiatric and behavioral disorders were encountered in four patients with psychotic features for two.

Three patients showed SL episodes and none were treated with antithrombotic medication. Patient p10 had episodes of sudden transient left hemiplegia without abnormal movements that began at the age of 30 months and occurred about two times a year. These episodes were her first neurological manifestations of SWS. Her epilepsy began at the age of 6, with left hemiclonic SE.

Neuro-radiological features (Table 4)

MRI with contrast was available for eight patients. A leptomeningeal enhancement was observed in seven patients, all in the occipital lobe (Fig. 1a). One patient had no enhancement on MRIs at both 56 and 65 years. The leptomeningeal enhancement was unilateral for six patients and bilateral but asymmetric for one. An extended hemispheric leptomeningeal enhancement was noted for three patients (Fig. 1b). No infratentorial enhancement was seen. A dural enhancement was observed in one patient (p7, Fig. 1b).

Brain calcifications were observed in eight patients. All patients with calcifications had occipital lobe calcifications and certain had other locations (Fig. 1c). Calcifications were unilateral for seven patients and bilateral for one. One patient had neither leptomeningeal enhancement nor brain calcifications.

Brain atrophy was seen in all ten patients, unilateral in eight patients and bilateral in two. The occipital lobe was affected in nine patients (with or without other lobes). One patient presented isolated frontal atrophy without occipital involvement. The patient p7 showed right major hemispheric leptomeningeal angioma, calcifications, and extensive bilateral, but mainly right, atrophy (Fig. 1b).

Dilated choroid plexus was observed in all patients, unilateral in eight (Fig. 1a) and bilateral in two. MRI showed deep venous dilation in four patients, unilateral and ipsilateral to leptomeningeal enhancement in two and bilateral in two others (Fig. 1d). Intracranial proximal vessels were normal in the three patients who had TOF sequences on MRI. No developmental venous anomalies were encountered in the eight patients who received gadolinium injection. Non-specific white matter abnormalities were observed in two patients (p6 and p7).

Three patients had a hippocampal atrophy, ipsilateral to other radiological abnormalities for all patients. In addition to hippocampal volume loss, p8 showed left hippocampal T2-weighted (Fig. 2a top) and T2-FLAIR (Fig. 2a bottom) hyper-signal consistent with a diagnosis of left HS, associated with clinical and EEG features of mesial temporal lobe epilepsy.

Two patients presented cerebellar atrophy. For p2, cerebellar atrophy was bilateral but asymmetric, more noticeable contralaterally to the side of most extensive supratentorial (including frontal) leptomeningeal enhancement and atrophy (Fig. 2b). For p7, it was unilateral and contralateral to supratentorial hemispheric (including frontal) leptomeningeal enhancement and atrophy (Fig. 2c).

Frontal sinus pneumatization was seen in six patients (Fig. 1a and b).

One patient (p1) benefited from a brain MRI during the 24 h following the first SE which showed an extended linear cortical hyper-signal on DWI and T2-FLAIR sequences ipsilateral to leptomeningeal angioma, consistent with postictal abnormalities that were no longer present on MRI at 3 months. MRI performed at the ages of 46 and 53 for p2, 56 and 65 for p3, 23 and 26 for p6, and 31 and 38 for p8 showed no changes. However, MRI performed at 51 and 54 years in p4 did show right occipital and temporal leptomeningeal enhancement that was no longer found on MRI performed at 65 and 69 years. Cerebral and cerebellar atrophy of p7 increased between MRI performed at 62 and 67 years of age. Furthermore, on the latter, we found numerous left hemispheric lobar micro-bleeds (Fig. 2d,

SWAN sequence) which were not present on the first MRI (GE sequence).

Electroencephalographical features (Online Resource 1)

EEG records were available for seven patients, including one long-term continuous video-EEG for pre-surgical evaluation of refractory epilepsy (p8).

Background amplitude asymmetry was observed in all EEG (mean ratio ipsilateral/contralateral of 0.62; range 0.43–0.88) and was particularly significant for p7 (Online Resource 2a). Asymmetric background frequency was found in most EEG (mean ratio ipsilateral/contralateral of 0.91; range 0.67–1). Slow waves were recorded over both hemispheres in five patients (Online Resource 2b), more notably over the hemisphere that was ipsilateral to leptomeningeal angioma. Interictal epileptiform activities were only recorded in two patients (Online Resource 2c). FS were recorded in two patients. EEG recorded during the acute phase of a SL for p7 showed numerous bilateral, but mostly left hemispheric, polymorphic delta slow waves without epileptiform activities.

Discussion

This study describes the clinical, neuro-radiological, and electroencephalographical features of ten adult patients with SWS treated in a tertiary Epilepsy Unit. Reports of the clinical course of SWS in adult patients with long-term follow-up are rare in comparison to numerous pediatric reports. Our work highlights the wide range of neurological symptoms of adult patients with SWS and their evolution over several decades.

In our cohort, despite the congenital facial port-wine birthmark, the absence of SWS diagnosis prior to their first neurological manifestations raises the issue of SWS screening for patients with suggestive dermatological findings [21]. Three locations of facial port-wine birthmarks have been reported with a higher risk of association with SWS [22]. More recent studies suggest that facial port-wine birthmark distribution follows the embryonic vasculature of the face rather than the trigeminal nerve. Thus, a higher risk of SWS is encountered in forehead, median, and hemi-facial phenotypes of port-wine birthmarks [21]. Imaging may be misleading for diagnosis as MRI abnormalities may be minor and typical imaging characteristics may be absent. Patient p3's MRI did not display leptomeningeal enhancement or brain calcifications, two imaging mainstays for neuro-radiological diagnosis of SWS. In patient p5, the right occipito-temporal leptomeningeal enhancement disappeared between the ages of 54 and 65 years. The natural history of the pial enhancement has never been reported in adults and elderly patients. An absence of leptomeningeal enhancement has already been reported in children when MRI is performed too early [5]. Delayed visualization of pial enhancement in children might be due to the leptomeningeal vessel dilation which is progressive in SWS [23]. Conversely, loss of pial enhancement in adults may be due to the regression of pial vessels secondary to cortical thrombosis [24]. SL episodes, mainly hemiplegia, are often reported by patients with SWS, and three patients in our cohort presented SL episodes. Precise mechanisms underlying these transient acute manifestations are still unknown. SL episodes are usually considered cerebrovascular events due to cortical ischemia secondary to recurrent thrombosis within the leptomeningeal angioma. None of the patients reported in our work had antithrombotic therapy. Antiplatelet treatment, such as low-dose aspirin, may be beneficial but no prospective randomized controlled trials, especially among adults, have been performed to demonstrate the safety and efficacy of aspirin in SWS.

Despite an extensive congenital facial angioma and very severe ocular abnormalities, patient p3's presentation was atypical. In addition to the lack of characteristic imaging findings, he did not have any focal neurological deficits, and he presented unusual late-onset GTCS. Late-onset epilepsy has been reported up to the seventh decade [7–13]. In most of these reports, seizures were controlled with an antiepileptic monotherapy, suggesting that these patients present less severe forms of SWS than the more common neonatal or childhood-onset forms. Our patient, however, required three AED to become seizure-free. Some authors have suggested that patients with late-onset epilepsy have a less extensive vascular injury and therefore less hypoxic brain damage [9]. This could explain the absence of leptomeningeal enhancement or calcifications in p3 but is contradictory with previous reports of late-onset epilepsy in which MRIs show typical imaging abnormalities.

Simple visual hallucinations suggestive of occipital seizures were reported in only one patient in our cohort, even though the occipital lobe was a localization for angioma in most of our patients. This is consistent with previous pediatric and adult cohorts [16, 25–27]. Moreover, occipital seizures are not limited to visual symptoms. The most common mode of propagation of occipital seizures is infrasylvian, with involvement of the ipsilateral temporal region, and temporal lobe semiology was the most frequent among our patients with FS. Most patients did not present initial symptoms of occipital seizures, and MRIs showed various temporal lobe abnormalities including pial enhancement, calcifications and/or atrophy.

An independent temporal epileptogenic focus was identified in one patient displaying typical radiological left HS and electro-clinical features of mesial temporal lobe epilepsy. The

Table 4 Main neuro-radiological features

No.	Leptomeningeal enhancement	Calcifications	Atrophy	Choroid plexus dilatation	Deep veins dilatation	Hippocampal atrophy	Radiological evolution
p1	Right O, P, T and F	Absent on MRI *No CT-scan available*	Right O, P, T and F	Right	Right, with brush aspect		Disappearance of right postictal abnormalities 3 months after 1st SE
p2	Right O, P, T and F Left O and P	Right P Left O	Right O, P, T and F Left O, P, T and F	Right and left	Right and left		Stable at 46 and 53 years
p3	Absent	Absent	Right O and P	Right		Right	Stable at 56 and 65 years
p4	Right O and T	Right O, P and T	Right O and P	Right			Disappearance of right LE at 65 and 69 years in comparison with MRI at 51 and 54 years
p5	*Only MRI and CT-scan without contrast*	Left O, P and T	Left O, P and T	Left			NA
p6	Right O and P	Right O	Right O and P	Right			Stable at 23 and 26 years
p7	Right O, P, T and F	Right O, P, T and F	Right O, P, T and F Left O, P and F	Right and left	Right and left		Appearance of left micro-bleeds and increased cerebral and cerebellar atrophy at 67 years in comparison with MRI at 62 years
p8	Left O	Left O and T	Left O and P	Left		Left, with T2 and T2-FLAIR hs	Stable at 31 and 38 years
p9	Right O, P and T	Right O	Right O	Right	Right	Right	NA
p10	*Only CT scan without contrast*	Right O, P and F	Right F	Right			NA

F frontal, *hs* hyper-signal, *LE* leptomeningeal enhancement, *NA* not available, *O* occipital, *P* parietal, *SE* status epilepticus, *T* temporal;
The significance of Italics values are represent the MRI or CT scan sequences, that are lacking

HS of this patient was ipsilateral to other MRI abnormalities, suggesting a link between the pathogenic processes involved in the brain injury related to SWS and the HS. Furthermore, two other patients in our cohort had hippocampal atrophy ipsilateral to other SWS abnormalities, illustrating the vulnerability of the ipsilateral hippocampus in SWS. The prevalence of HS in SWS is unknown, and it has been reported only in two patients [28, 29]. Various mechanisms may induce acute or chronic damage in amygdala–hippocampus structures in SWS. The HS could be secondary to repetitive epileptic seizures, originating from a neocortical injury caused by the vascular malformation, outside of the temporal lobe. Moreover, leptomeningeal vascular malformation may cause chronic hypoxic injury of underlying brain parenchyma. This malformation has been generally described in the occipito-parietal area and rarely in the temporal area. However, MRI does not have a 100% sensitivity in detecting pial angioma. Functional imaging studies have displayed perfusion and metabolic abnormalities beyond lobes affected by visible leptomeningeal vascular malformations [30], and surgical reports have shown leptomeningeal angiomatosis visible over brain regions where MRI failed to reveal pial enhancement [29]. Thus, it seems possible that the cerebral vascular malformation extends to include the temporal lobe but is too subtle to be revealed on contrast MRI sequences, and may lead to chronic temporal lobe parenchyma hypoxia, in particular amygdala-hippocampus hypoxia. Finally, the HS may result from the absence of a functional cortical venous drainage system,

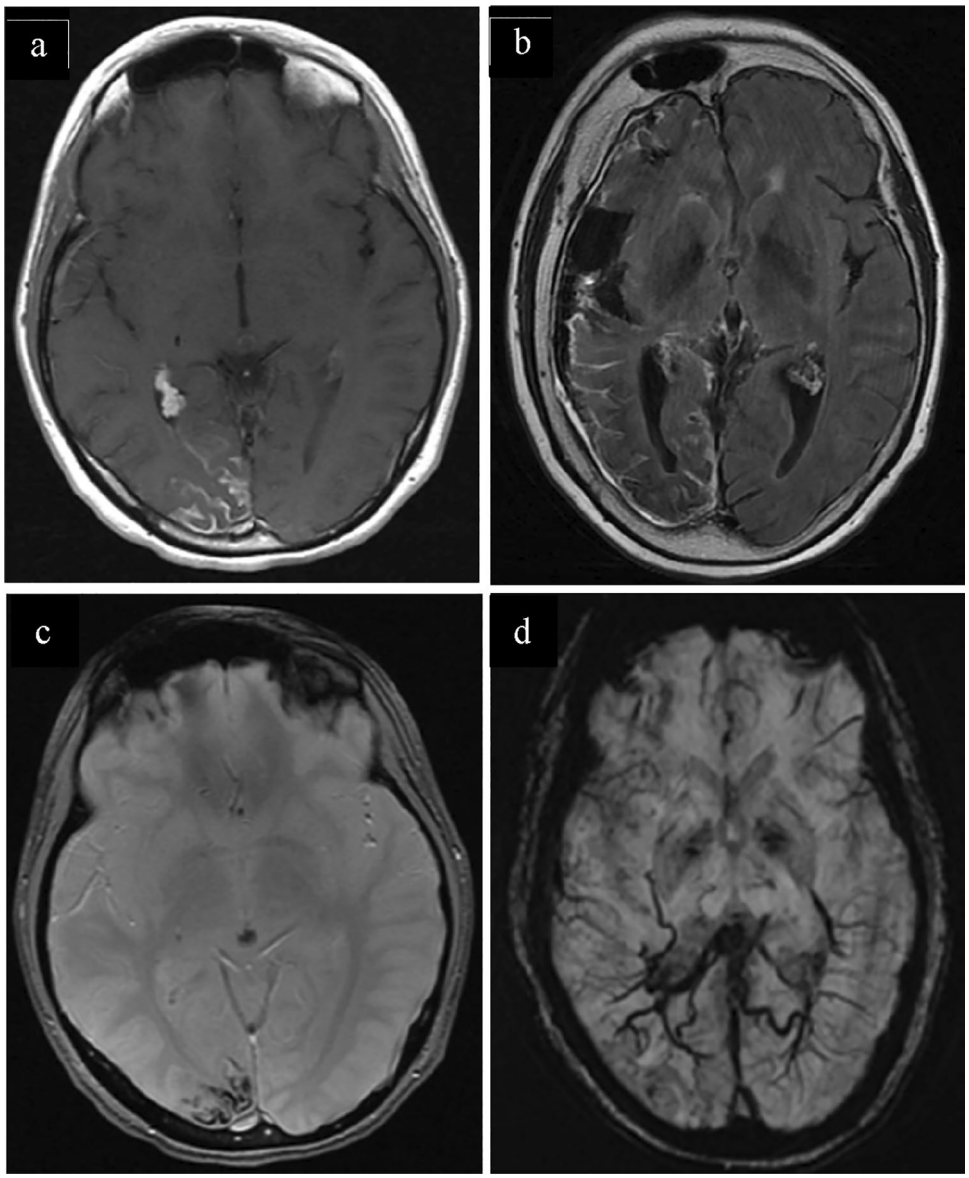

Fig. 1 Typical brain MRI findings in SWS. **a** right occipital leptomeningeal enhancement, choroid plexus dilatation and frontal sinus pneumatization (p6). **b** right extended leptomeningeal and dural enhancement, hemispheric atrophy and frontal sinus pneumatization (p7). **c** right occipital calcifications (p6). **d** bilateral deep vein dilation (p2)

leading to abnormal drainage through the deep venous system, causing choroid plexus dilation by venous blood accumulation and raised pressure [31]. Considering the vascularization of the hippocampus, the chronic elevated pressure in the choroid plexus may cause hippocampal hypoxia, leading to HS [32].

Electroencephalographical features of our patients are concordant with previous reports [17]. Moreover, we found bilateral slowing which was more pronounced in the hemisphere ipsilateral to leptomeningeal angioma. This bilateral slowing could result from hypoxia in the ipsilateral hemisphere, as a result of the leptomeningeal vascular malformation and repetitive ictal activity, but also in relation to hypoxia in the contralateral hemisphere, probably from a vascular steal phenomenon [33].

Neuro-radiological follow-up of our patients showed unique features that have, to our knowledge, never been described in SWS. Patient p7 presented a severe form of SWS. We were able to collect information over a very long follow-up, the longest reported to date, from early childhood to her death at 71 years of age. An MRI performed at 67 years showed numerous lobar and cortical micro-bleeds extending over the left hemisphere, contralateral to the leptomeningeal angioma. These micro-bleeds were not observed on an MRI performed 5 years earlier, but the T2 GE sequence from the earlier MRI has a lower sensitivity than the SWAN sequence from the later MRI. The combination of dementia with cerebral atrophy and lobar micro-bleeds suggests cerebral amyloid angiopathy, but neither intracranial hemorrhage nor cortical superficial siderosis, usually described in cerebral amyloid angiopathy, was observed [34]. Furthermore, these micro-bleeds were located in only one hemisphere which is atypical for cerebral

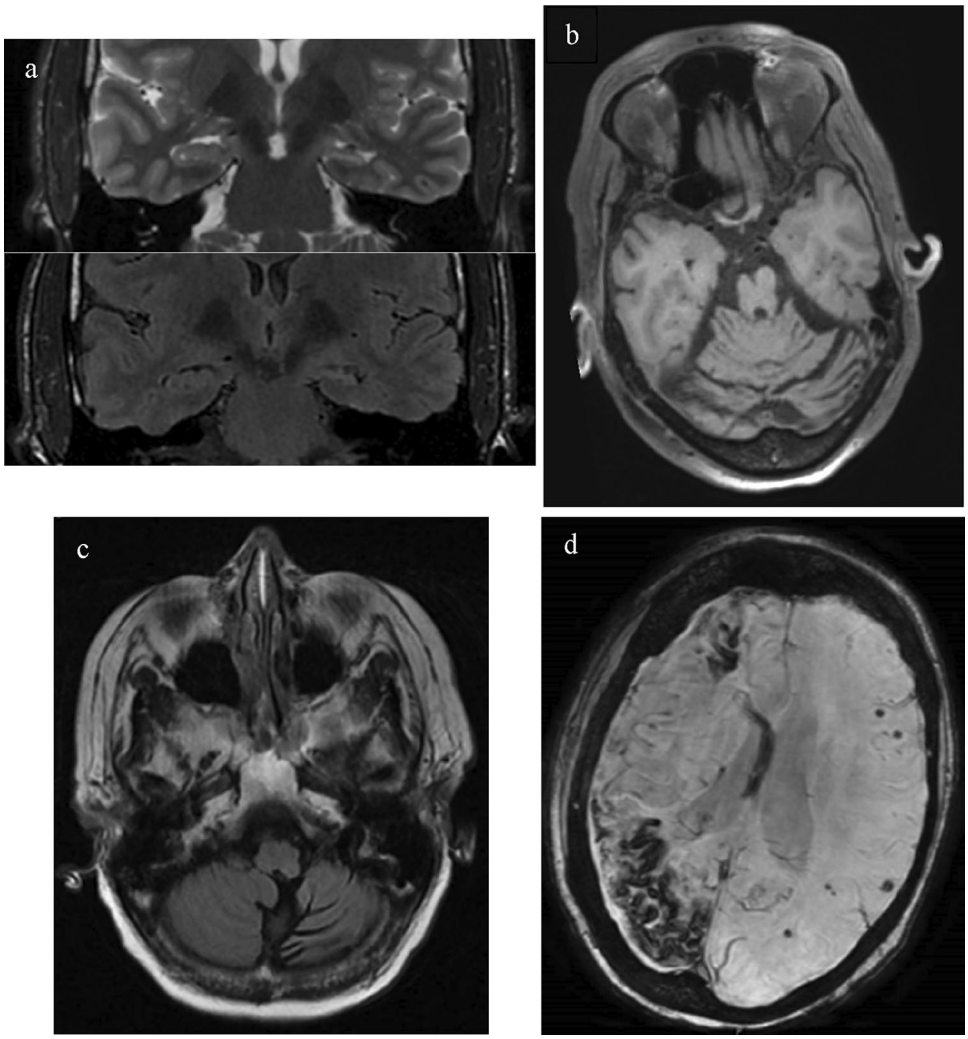

Fig. 2 Unusual brain MRI findings in SWS. **a** left hippocampal sclerosis (p8). **b** asymmetrical bilateral cerebellar atrophy slightly more conspicuous in the left cerebellar hemisphere (p2). **c** unilateral left cerebellar atrophy (p7). **d** left hemisphere micro-bleeds contralateral to SWS-related radiological abnormalities (p7)

amyloid angiopathy. Large cohorts of patients suffering from SWS have shown a progressive increase in brain atrophy and calcifications, but these cohorts have only included children or young adults [26, 35]. Fifty-two adult patients have been reported but without neuro-radiological findings [16]. Long-term follow-up on elderly patients with SWS and longitudinal reports are necessary to better assess the clinical and neuro-radiological course of this syndrome.

We also identified a rare imaging pattern in SWS: contralateral cerebellar atrophy in relation to supratentorial leptomeningeal angioma, which could be explained by crossed cerebellar diaschisis [36]. This phenomenon occurs with supratentorial lesions, generally frontal [37], and has been widely described in various central nervous system diseases, such as ischemic stroke [38], intracranial hemorrhage [39] and brain tumors [40]. Crossed cerebellar diaschisis has also been reported after seizures [41] and SE [42]. More recently, functional [24, 43, 44] and structural [23, 45] cerebellar abnormalities have been reported in SWS. Both of our patients with cerebellar atrophy had contralateral supratentorial frontal angioma and atrophy. Two other patients in our cohort had supratentorial frontal lesions, but neither patient had cerebellar atrophy on imaging. These patients may present metabolic or perfusion abnormalities that have not been detected on imagery and cerebellar atrophy may be detected in the long-term on neuro-radiological follow-up.

Our study offers a large overview of adult patients with SWS whose neurological courses extend over many years or decades. We collected data from ten adult patients, offering a wide spectrum of multimodal neurological histories. However, our work has some limitations. All patients had seizures and were treated in a reference center for Rare Epilepsy. Therefore, they are not representative of the whole population of SWS adult patients and may represent a more severe subgroup of patients. Our cohort included a majority of women, whereas the sex ratio in SWS is one. All data were gathered retrospectively, through review of medical records which is a source a bias. These limitations emphasize the need for a prospective long-term cohort to better

understand the natural course of SWS in all age groups. Cellular and animal models, the development of new biomarkers, and innovative clinical trials may offer future therapeutic strategies to better treat patients suffering from SWS, in particular adult patients who are at risk for various disabilities related to SWS progression.

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Declarations

Conflicts of interest The authors have no competing interests to declare that are relevant to the content of this article.

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