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Original Article

Flunarizine for Headache Prophylaxis in Children With Sturge-Weber Syndrome

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ABSTRACT

Background: Children with Sturge-Weber syndrome can experience severe headache with or without transient hemiparesis. Flunarizine, a calcium antagonist, has been used for migraine. The experience with flunarizine for headache in a cohort of children at a national center for Sturge-Weber syndrome is reviewed, reporting its efficacy and adverse effect in this population.
Methods: We collected data from health care professionals' documentation on headache (severity, frequency, duration) before and on flunarizine in 20 children with Sturge-Weber syndrome. Adverse effects reported during flunarizine treatment were collated. The Wilcoxon signed rank test was used to determine the significance of pre- versus post-treatment effect.
Results: Flunarizine was used for headache alone (13) or mixed migrainous episodes and vascular events (7). The median duration of treatment was 145 days (range 43 to 1864 days). Flunarizine reduced headache severity ($z = -3.354$, $P = 0.001$), monthly frequency ($z = -2.585$, $P = 0.01$), and duration ($z = -2.549$, $P = 0.01$). Flunarizine was discontinued owing to intolerable adverse effects in a minority (2). Sedation and weight gain were the most common side effects. There were no reports of behavior change or extrapyramidal features.
Conclusions: The most effective management for headaches in patients with Sturge-Weber syndrome has not been established. This retrospective observational study found benefit of flunarizine prophylaxis on headache severity, frequency, and duration in children with Sturge-Weber syndrome without severe side effects. Flunarizine is not licensed for use in the United Kingdom, but these data support its off-license specialist use for headache prophylaxis in Sturge-Weber syndrome.

Introduction

Sturge-Weber syndrome (SWS), a mosaic vascular neurocutaneous disorder, caused by a somatic mutation in GNAQ, is estimated to affect 1:20,000 to 1:50,000 children.[1,2] The disorder classically comprises leptomeningeal capillary venous vascular malformations as well as a facial port-wine capillary angioma of the forehead or eyelid in most.[3,4] The occipital and parietal lobes are predominantly involved, with bi-hemispheric involvement in about one-sixth of the children.[5] A complex pattern of disability is observed owing to ocular changes in 30% to 70%[6,7] and neurological sequelae in most individuals. Neurological manifestations include epilepsy in 75% of patients with unilateral brain involvement and 95% of patients with bilateral brain involvement,[8,9] hemiplegia in one-third,[10] transient stroke-like episodes in up to 75%[11] (with aspirin reducing the number of attacks in affected patients by two-thirds[12]), hemianopia in 40%,[13] and intellectual disability (intelligence quotient [IQ] < 70 in 15% to 64%; IQ: 70 to 85 in 11% to 21%).[4,14] Psychiatric disturbance is common, with mood disorder in 30%, disruptive behavior disorder in 25%, adjustment disorder in 25%, and attention-deficit/hyperactivity disorder in 20% to 40%.[11,15]

Children with SWS also have a high prevalence (30% to 45%) of recurrent headaches.[16-18] The prevalence of a formal diagnosis of migraine in children with SWS (28%, with no gender disparity[17])

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exceeds that in the general population (5% in males, 17% in females[19]). Migraine is a statistical risk factor for transient ischemic attacks and strokes in the adult and adolescent populations.[20,21] In SWS, headache has been attributed to vasomotor disturbances within and around the angioma[22] and is reported as an accompaniment to some cases of cortical vein thrombosis in SWS.[23] These studies suggest that headache prevention and appropriate management in patients with SWS might be an important aspect of their clinical care for reasons other than symptomatic relief. In practice, standard advice includes the avoidance of head trauma and any other identified triggers such as diet and stress. Simple analgesia is useful for relieving moderate headaches, and recurrent severe headaches are an indication for prophylactic treatment.

A recent consensus statement on the management of SWS highlighted headache as a significant unaddressed problem.[24] The evaluation of headaches in patients with SWS requires a good general pediatric multidisciplinary approach[25] and investigation of acute causes of headache related to SWS. These include acute glaucoma, seizures (including electrical seizures only), cerebrovenous occlusion, and intracranial hemorrhage.[26-29] Patients with SWS are also disposed to headaches that are situational or relate to a mood disorder. There is little published information on the effectiveness and adverse effect profile of different prophylactic treatment agents for headaches in SWS. A principled approach to prophylaxis would target the pathogenesis of migraine and recognize pharmacologic differences among potential agents. The emergence of migraine symptoms is postulated to reflect cerebral microvascular hypoxia,[30] which depresses synaptic function.[31] Calcium channel blockers inhibit this synaptic depression under hypoxia[32] and relax vascular smooth muscle, preventing cerebral vasospasm-induced ischemic hypoxia.[33] The ideal agent of this class should penetrate the blood-brain barrier well without impairing normal cerebral arteriolar autoregulation or reducing blood pressure. Flunarizine and nimodipine meet these criteria best.[34] Flunarizine is, however, a more potent and persistent inhibitor of hypoxic synaptic depression than other calcium channel inhibitors.[35]

The preceding information provides a rational basis for considering a potential clinical role for flunarizine in migraine prophylaxis in SWS. There is some evidence of its safe use and benefit in the prophylactic treatment of childhood migraine[36,37] and hemiplegic migraine,[38] notwithstanding its lack of regulatory approval in the United Kingdom or the United States. The intractable nature of migrainous headaches in children with SWS motivated the use of flunarizine for headache prophylaxis in our specialist service for patients with SWS in the United Kingdom. This retrospective observational review describes the effect and tolerability of flunarizine in this population.

Methods

We reviewed the medical records of all patients under the SWS service at Great Ormond Street Hospital who were on flunarizine treatment. The center holds comprehensive neurodisability reports from medical and multidisciplinary allied health professional (psychology, occupational therapy, speech and language therapy, physiotherapy) assessments of patients with SWS. Collateral sources of information were considered, including documented e-mail or telephone correspondence between parents, patients or schools, and the clinical nurse specialists for the SWS service. Headache data were captured from the clinical documentation of parent and patient reports. This review considered the worst rating of headache severity, frequency, and duration before the initiation of flunarizine and compared this with the worst rating of the same headache parameters at the latest clinic follow-up after treatment was commenced.

Headache severity was scored using a headache severity scale. This scale permits classification based on parent reports in children whose verbal communication is impaired. The scale has three grades: Grade I (mild: child is able to continue daily activities), Grade II (moderate: child is able to continue daily activities with limitation), and Grade III (severe: child is unable to continue daily activities). The headache before commencement of flunarizine was compared with that following treatment. In instances wherein a reduction of headaches was reported on flunarizine, the post-treatment headache was coded on the severity scale as one categorical level below the pretreatment headache. *Headache frequency* was the total number of headaches experienced in one month irrespective of the severity. *Headache duration* was categorized as short duration (less than one hour), intermediate duration (one to 4 hours), long duration (four to 24 hours), or protracted (more than 24 hours).

The established side effects of flunarizine treatment were ascertained from the clinical records. Owing to the long-term health risk associated with excessive weight gain in childhood, the occurrence of significant weight gain on flunarizine was sought, and this was defined as weight increase of two or more adjacent lines on the World Health Organization growth charts for males and females aged 2 to 18 years.[39] The Wilcoxon signed rank test was used to determine significant difference between pretreatment versus post-treatment headache.

Results

Demographics

Patient characteristics are shown in Table 1. The 20 patients (11 female) ranged in age from three to 17 years (mean 10.5 years). The mean age of headache onset was seven years (range: five months to 15 years). At the time of the study, 18 patients continued to take flunarizine.

Clinical details

SWS was confirmed with clinical features and pial enhancement on gadolinium contrast brain magnetic resonance imaging (MRI) in all patients. The port-wine stain was present in 15 patients (bilateral in five, left in seven, right in three). Pial angiomatosis was bilateral in seven children. The number of lobes affected was one (12 patients) or two (eight patients). Other MRI findings were parenchymal calcification (eight cases) and developmental venous anomalies (eight cases). The patient cognitive profile (American Psychiatric Association 2013)[40] showed IQ within the average range in 10, mild intellectual disability range (IQ: 50 to 70) in seven, moderate intellectual disability range (IQ: 35 to 49) in one, and severe intellectual disability range (IQ: 20 to 34) in two. The clinical findings regarding permanent motor deficit were no motor deficit in 14, hemiplegia in five, and quadriplegia in one. Comorbidities were epilepsy (18) and glaucoma (12).

Headaches

The indication for flunarizine was headache alone (13) or associated with transient hemiparetic episodes ("headache-plus," 7). The headache-alone group had the characteristic migrainous features—pulsatile, visual aura, photophobia, phonophobia, exacerbated by head movement, and associated with nausea—in six of 13 (46%). The headache-plus group showed these features in two of seven (29%). This difference was not statistically significant.

Headache was severe in the majority of children (13) and moderate in the remainder. Frequency ranged from one per month to up to 60 per month. Duration of headache ranged from 10 minutes per episode to several days. A statistical association was not observed between headache parameters (severity, frequency, duration) and radiological findings (number of lobes affected by pial angioma, bilateral involvement, presence of venous anomalies, presence of calcification).

Headaches and transient neurological deficits (headache-plus)

There were transient neurological symptoms with headaches, presenting with hemiparesis in seven cases, and associated with sensory disturbances (paresthesias and numbness) in three cases. The onset was subacute (over hours, often overnight) with spontaneous resolution over 24 to 48 hours in the pretreatment phase. Some episodes were reported to have been triggered by minor head injury (Patients 5, 18, 20).

The mean age of the headache-only group was older than that of the headache-plus group (11.7 years versus 7.7 years, $t = 2.396$, $P = 0.03$). There were otherwise no differences in radiological, headache (severity, frequency, duration), or therapeutic characteristics between the two groups.

Doses of flunarizine

Children took flunarizine at a starting dose of 5 mg per day with titration based on symptom response to 10, 15, or 20 mg/day. The twice daily dosing schedule was used at the maintenance phase when the total daily dose was 10 mg per day or greater (13 children). The median duration of treatment was 145 days (range 43 to 1864 days).

TABLE 1.
Patient Characteristics

Case	Sex	Age (years)	Indication	Specific Features*	Facial Port-Wine Stain	MRI	Cognition/Motor Deficit	Concurrent Anticonvulsant Treatment
1	F	12	Headache	Yes	Left	Bilateral pial angioma calcification	Severe ID quadriplegia	CBZ, TOP
2	F	8	Headache	Yes	Bilateral	Unilateral pial angioma calcification	Mild ID hemiplegia	CBZ, TOP, CLO
3	M	7	Headache + transient hemiparesis	No	Bilateral	Bilateral pial angioma	Average IQ	LEV, VPA
4	F	11	Headache	No	None	Unilateral pial angioma ipsilateral HS calcification	Average IQ	LEV, LTG
5	F	5	Headache + transient hemiparesis	No	Bilateral	Bilateral pial angioma	Mild ID hemiplegia	LEV, OXC
6	M	10	Headache + transient hemiparesis	No	None	Unilateral pial angioma	Mod ID hemiplegia	LTG, PER, CLN
7	F	14	Headache	Yes	Left	Unilateral pial angioma calcification DVA	Average IQ	LTG
8	F	13	Headache + transient hemiparesis	Yes	Right	Unilateral pial angioma DVA	Average IQ	None
9	M	15	Headache	No	Bilateral	Bilateral pial angioma	Mild ID	LTG
10	F	7	Headache	No	Right	Unilateral pial angioma calcification DVA	Average IQ	LEV, OXC
11	F	16	Headache	No	Left	Unilateral pial angioma	Average IQ	LEV, TOP, CLO
12	M	3	Headache	No	Right	Bilateral pial angioma DVA	Severe ID hemiplegia	LEV, TOP, CLO
13	F	14	Headache	Yes	Bilateral	Bilateral pial angioma DVA	Average IQ	LEV
14	M	9	Headache	Yes	None	Unilateral pial angioma calcification	Average IQ	LEV
15	M	10	Headache	No	Left	Unilateral pial angioma calcification DVA	Mild ID	None
16	F	13	Headache + transient hemiparesis	No	Left	Unilateral pial angioma ipsilateral HS calcification DVA	Average IQ	LEV
17	M	4	Headache	Yes	None	Unilateral pial angioma ipsilateral HS calcification	Average IQ	LEV, TOP
18	M	17	Headache + transient hemiparesis	Yes	Left	Unilateral pial angioma	Mild ID	LEV, CBZ
19	F	8	Headache	No	None	Unilateral pial angioma	Mild ID	LTG
20	M	5	Headache + transient hemiparesis	No	Left	Bilateral pial angioma DVA	Mild ID hemiplegia	LEV

Abbreviations:
CBZ = Carbamazepine
CLN = Clonazepam
CLO = Clobazam
DVA = Developmental venous anomalies
ESX = Ethosuximide
F = Female
HS = Hippocampal sclerosis
ID = Intellectual disability (IQ < 70: mild, 50 to 70; moderate, 35 to 49; severe, 20 to 34)
IQ = Intellectual quotient
LEV = Levetiracetam
LTG = Lamotrigine
M = Male
OXC = Oxcarbazepine
PER = Perampanel
TOP = Topiramate
VPA = Sodium valproate
ZON = Zonisamide
The key characteristics of SWS children treated with flunarizine.
* Specific migraine features: pulsatile headache, nausea, vertigo, photophobia, photophobia.

Flunarizine and headaches

Flunarizine reduced headache frequency in the sample (pre-treatment median eight per month versus a post-treatment median of less than one per month; Wilcoxon test $z = -2.585$, $P = 0.01$), reflecting 15 patients experiencing a decrease in headache frequency. Headache duration shortened on treatment in the sample from a median in the protracted (more than 24 hours) category to a median in the short-duration (less than one hour) category (Wilcoxon test $z = -2.549$, $P = 0.011$), representing shortened headaches reported in 14 patients. Flunarizine reduced headache severity category (Wilcoxon Test $z = -3.354$, $P = 0.001$). Headache characteristics before and on treatment with flunarizine are shown in Table 2. The headaches were abolished on treatment in five children: three female (Patients 4, 10, and 13) and two male (Patients 9 and 15). There were no significant statistical differences identified between patients who became free of headache and the rest of the sample. The benefit of flunarizine on headache was observed within the first month of treatment. Figs 1 and 2 show the reported effect of flunarizine on headache.

Flunarizine adverse effects

The spectrum of symptoms experienced by children on flunarizine treatment is shown in Table 3. See the on line supplementary Appendix for further details regarding adverse effects (Table 4).

Flunarizine discontinuation

Flunarizine was discontinued in two children, because of intolerable sedation (1) and a nonanaphylactic allergic reaction (1) 10 days after starting adminstration.

Concurrent medication

Aspirin or another antiplatelet agent was used in 19 patients, and regular anticonvulsive medication in 18 patients. The three most common anticonvulsants were levetiracetam (12), lamotrigine (5), and topiramate (5). Topiramate prophylaxis for headaches was trialed and discontinued before flunarizine in a further four children.

Discussion

Patients in this study were investigated and classified as having "headache attributed to encephalotrigeminal or leptomeningeal angiomatosis" (ICHD III: 6.3.5).[41] Facial port-wine stain was present in most (unilateral in half, bilateral in one-quarter), and absent in one-quarter. The representation of SWS without facial port-wine stain in this sample, compared with about 5% in the literature,[4] is notable but unexplained. General cognitive function in most patients was either within the low average or mild intellectual disability range, but most patients were free of pre-existing permanent motor deficit (hemiplegia or quadriplegia). Two clinical headache presentations were recognizable: headaches with associated sensory auras and headaches with episodes of transient hemiparesis. In this cohort, the latter were younger on average (statistically significant) and there was a trend (not statistically significant) toward their headaches not showing migrainous characteristics. The brain MRI and overnight electroencephalographic telemetry performed to investigate the two headache presentations did not find evidence of acute ischemia or electrical status epilepticus. The radiological features and therapeutic outcome was similar for the two presentations. Brain MRI findings were not a reliable predictor of headache burden, cognitive function, or motor deficit in this cohort. The incidence of developmental venous anomalies was 40% (8/20) in the present study. These data agree with the literature: around 45% of children with SWS demonstrate abnormalities in cerebral venous structures on gadolinium contrast MRI.[42] There was a similar incidence (40%, 8/20) of parenchymal calcification on MRI as reported in other cohorts of patients with SWS.[43] The spectrum of brain MRI changes in patients with SWS under our service has been reported elsewhere.[44]

An improvement of headache (severity, frequency, and duration) was reported during treatment with flunarizine. This therapeutic benefit was achieved with an acceptable adverse effect profile, consistent with previous use of flunarizine.[37] Flunarizine did not produce serious side effects. The common side effects were sedation and weight gain, which occurred at a higher rate than in the Peer et al. study of patients without SWS.[38] Sedation was reported in 10 of 20 (50%) in this study versus two of 72 (3%), and increased appetite or weight gain was reported in nine of 20 (47%) here versus five of 72 (7%).[38] Patients with SWS on flunarizine typically showed weight gain without reporting increased appetite. The differences in the side effect rates between the two studies might reflect the distinct features of patients with SWS as a group: brain structural change, epilepsy, and learning difficulties. Flunarizine is 90% bound to plasma proteins,[45] so concurrent treatment with aspirin and some anticonvulsants could also produce higher plasma flunarizine levels (through displacement) when compared with the Peer et al. study.[38] Plasma flunarizine levels were not measured in this cohort. Flunarizine was discontinued in one-

TABLE 2.
Headache Characteristics Before and on Treatment With Flunarizine

Headache Parameter	Mean (SEM)	Median	Wilcoxon Test	
			z	*P*
Headache Severity Grade			−3.354	0.001
Before	2.88 (0.125)	3		
On	0.88 (0.350)	1		
Headache Monthly Frequency			−2.585	0.01
Before	20.88 (4.15)	8		
On	5.63 (0.263)	1		
Headache Duration (hours)			−2.549	0.011
Before	2.88 (0.35)	3		
On	0.88 (0.125)	1		

Headache characteristics before and on treatment with flunarizine.

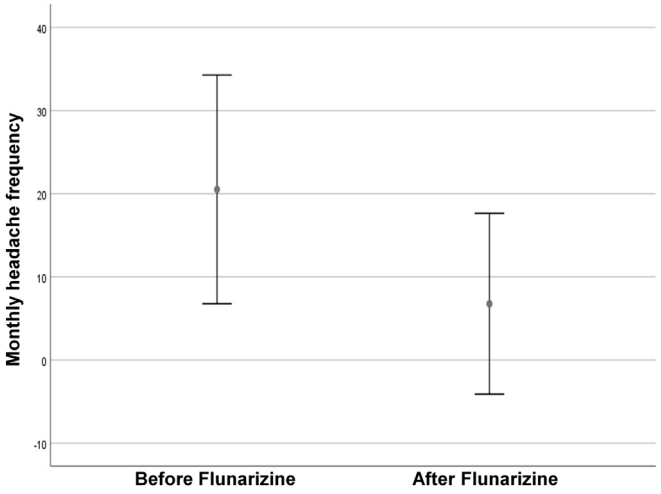

FIGURE 1. Headache monthly frequency before and after treatment with flunarizine.

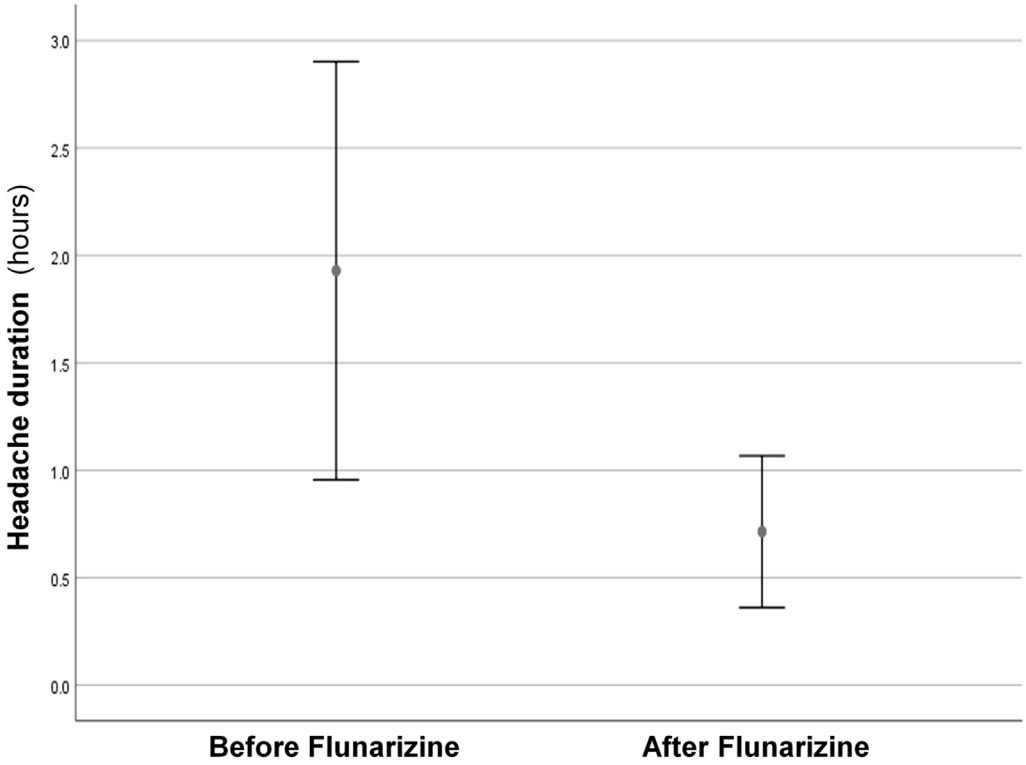

FIGURE 2. Headache duration in hours before and after treatment with flunarizine.

tenth, with median treatment duration of around a year (378 days), which compares well to the roughly one-fifth annual discontinuation rate of flunarizine in children with migraine without SWS.[38]

Flunarizine was associated with complete remission from episodes of transient hemiparesis in two children. Pretreatment transient hemiparesis episodes were often unprovoked, although in three patients at least one episode followed minor head trauma. Minor head trauma has been previously reported as a precipitating factor for transient hemiparesis in one-fifth of SWS cases.[46] The cause of unprovoked, recurrent transient hemiparesis inthis study, wherein patients with SWS are on antiplatelet treatment and anticonvulsants, is undetermined.[47] Some authors propose that the episodes might be an unusual form of seizure (an ictal paresis) that is not detectable on scalp electroencephalography but shows an ictal signature on 99mTc-hexamethylpropylene amine oxime single-photon emission computed tomography.[48] The latter technique was not performed as part of the investigation of the clinical presentation in this cohort. A second notion is that these are transient ischemic episodes in patients who would otherwise have developed ischemic stroke without antiplatelet treatment. Strokes are a neurological emergency in children with SWS, commonly presenting with severe headache, encephalopathy, and progressive focal deficits, often accompanied by status epilepticus.[49] The acute MRI features are ischemic change, infarction, and cerebral edema.[50,51] The patients in this study did not present with these radiological features. This fact does not preclude the possibility of similar mechanisms for the headache and clinical features in our patients, including acute rise in intracranial pressure from microvascular stasis, meningeal irritation from vascular leakage around the angioma, and hyperperfusion of some areas due to anomalous cerebral autoregulation (which also produces a “steal” phenomenon).[52,53] It is unclear if flunarizine produced remission from transient hemiparesis in the two children through a neuroprotective effect. A potential neuroprotective effect of flunarizine in SWS would be expected to slow the progression of pathologic structural change of the brain parenchyma (atrophy, calcification).[12] Longitudinal prospective work is required to evaluate this further.

Our patients experienced headaches while on anticonvulsant agents that are known to be effective in migraine, in keeping with expert opinion that the headaches in SWS are often difficult to control with standard measures.[24] There are concerns among some clinicians regarding the side effects of standard migraine treatments if applied to patients with SWS. For example, triptans were used by only one-fifth in a survey of 74 patients with SWS with migraine.[16] This could be a misinterpretation of the pre-existing

TABLE 3.
Headache Severity Grade

Headache Severity	Before	After
No Headache	0	5
Grade I (mild)	3	12
Grade II (moderate)	9	2
Grade III (severe)	8	1

The number of patients with each grade of headache and free from headaches before and on treatment with flunarizine.

TABLE 4.
Adverse Effects on Flunarizine

Adverse Effect	Number of Patients
Sedation	10
Weight gain	7
Gastrointestinal upset (nausea, bowel habit change)	3
Mood change	2
Seizure	1

The adverse effect profile of flunarizine.

two-fold baseline risk of stroke in adult migraineurs before using triptans.[20,54] Flunarizine might provide an acceptable option to improving the treatment of migraine-like headaches in children with SWS where clinicians and families hold such concerns regarding adverse effects. A practical hurdle to realizing the therapeutic benefit of flunarizine is that it is not approved for use in the United Kingdom, the United States, and several other countries, and this raises the question of whether other licensed calcium channel blockers might be suitable. There are a number of significant pharmacologic differences. Flunarizine is neuroactive with limited vascular effect and a long elimination half-life (18 days in adults without concurrent medication).[33-35,45] Most other calcium channel blockers are primarily vasoactive substances[33-35,45] and from a therapeutic perspective are of little empirical benefit for migraine prophylaxis,[55,56] although verapamil appears effective in aborting acute headache during hemiplegic migraine attacks.[57,58] There is a theoretical risk of vasoactive calcium channel blockers affecting cerebral perfusion in SWS by impairing cerebrovascular autoregulation and reducing systemic blood pressure, resulting in neurological deficits through a "steal" phenomenon.[59,60] Patients in this study did not receive licensed calcium channel blockers, and firm judgment cannot be made at this time regarding their effect in patients with SWS with headache.

Limitations

The limitations of this study are its retrospective observational design and modest sample size. The study design was pragmatic, given that a double-blinded randomized controlled trial is not very feasible in a rare disorder. Standardized headache questionnaires, such as the PedMIDAS,[61] were not used owing to not having been validated in the SWS population.

Conclusion

There is no previous published study of headache prophylaxis in children with SWS. Two presentations of paroxysmal headaches were identified in SWS that might represent a clinical spectrum. Flunarizine prophylaxis for both forms of headache in children with SWS might reduce the severity, frequency, and duration. Flunarizine treatment is well tolerated, with some risk of sedation and weight gain. These usually do not result in drug discontinuation. Therapeutic data such as those presented here are valuable to the clinician. Flunarizine is currently unlicensed in the United Kingdom for children but can be considered in patients with SWS with recurrent moderate to severe headaches. The present work does not permit a definite conclusion to be drawn regarding whether benefit for headaches with transient hemiparesis in SWS reflects a potential neuroprotective effect of flunarizine.[31,62]

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2018.11.012.

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