

Central Hypothyroidism and Sturge-Weber Syndrome

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Sturge-Weber syndrome is a rare disorder manifesting with a facial port-wine birthmark and a vascular malformation of the brain. Infants and children present with seizures and stroke-like episodes with focal neurologic deficits. Our previous investigations revealed that growth-hormone deficiency occurs with an increased prevalence in Sturge-Weber syndrome, presumably secondary to involvement of the hypothalamic-pituitary axis. We have continued to screen for hormonal abnormalities in patients with Sturge-Weber syndrome, specifically those from our multidisciplinary center for patients with this condition. We describe 2 children out of 83 (2.4%) with Sturge-Weber syndrome and brain involvement who were evaluated at our center and diagnosed with central hypothyroidism, based on clinical signs and laboratory findings. This prevalence is much higher than that of central hypothyroidism in the general population. Although it is well-known that anticonvulsants can lead to abnormalities in thyroid function tests, including central hypothyroidism, patients with Sturge-Weber syndrome carry the additional risk of developing hypothalamic-pituitary dysfunction, secondary to their central nervous system dysfunction. Therefore, it is important that patients with Sturge-Weber syndrome undergo routine thyroid-function testing, especially in the face of any clinical manifestations. © 2008 by Elsevier Inc. All rights reserved.

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Introduction

Sturge-Weber syndrome is a congenital, sporadic disorder with vascular malformations of the brain, skin, and eye [1], occurring in approximately 1 in 20,000 live births. Impaired venous drainage and cerebral blood flow through the abnormal hypoplastic cortical vessels, leptomeningeal vessels, and venous draining vessels result in cortical atrophy, calcification, and injury [1]. Most children with Sturge-Weber syndrome present in the first few years of life with seizures, stroke-like episodes, developmental delays, hemiparesis, and visual-field deficits [2]. Based on information from the Sturge-Weber Foundation, and because Sturge-Weber syndrome affects the central nervous system, we suspected that patients affected with this condition would be at risk for abnormalities of the hypothalamic-pituitary axis. Recently, we described an increased prevalence of growth-hormone deficiency in a subgroup of patients with Sturge-Weber syndrome, i.e., 18-fold higher than in the general population [3]. Here we report on 2 cases of patients with Sturge-Weber syndrome at our clinical center (2.4% of total Sturge-Weber syndrome patients with brain involvement seen at the Hunter-Nelson Sturge-Weber Center, Baltimore, MD) who demonstrate central hypothyroidism, based on clinical signs and laboratory findings. This is a markedly increased prevalence of central hypothyroidism compared with the general population's prevalence of approximately 0.0002-0.005% [4-8]. These cases stress the importance of following thyroid-function studies in patients with Sturge-Weber syndrome.

Methods

We determined the total number of patients with Sturge-Weber syndrome and definite brain involvement seen at the Hunter Nelson Sturge-Weber Center from 2000-2007. From these subjects, we identified 2 children who were diagnosed with central hypothyroidism while in our care. We also determined from the database the percentage of subjects with Sturge-Weber syndrome and brain involvement with a maternal history of either hypothyroidism or hyperthyroidism, based on intake

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Table 1. Characteristics of subjects with Sturge-Weber syndrome and central hypothyroidism

Subject	Age	PWS Side	Glaucoma	Hemiparesis and Stroke-like Episodes	Brain Leptomeningeal Involvement	CNS Medications on Diagnosis of Central Hypothyroidism
Subject 1	7 yr	Right	Right	Yes	Right temporal, parietal, and occipital	Oxcarbazepine, topiramate, and low-dose aspirin
Subject 2	12 yr	Left	Left	Yes	Left frontal, temporal, parietal, and occipital	Oxcarbazepine, Risperdal, low-dose aspirin, and vagal nerve stimulator

Abbreviations:

CNS = Central nervous system

PWS = Port-wine stain

questionnaires. This study received approval from the Johns Hopkins University School of Medicine Institutional Review Board.

Results

Eighty-three patients with Sturge-Weber syndrome and documented brain involvement were seen at our Sturge-Weber Center between 2000-2007 (38 females, 45 males; mean age, 10.6 years; range, 0-57.5 years). Of these 83 patients, 2 children (2.4%, one male and one female; **Table 1**) were diagnosed with central hypothyroidism while in our care, based on laboratory studies and clinical signs. Sixty-four patients were children aged less than 18 years, resulting in a prevalence of 2/64 or 3.1% of the children with Sturge-Weber syndrome brain involvement exhibiting central hypothyroidism. Based on intake questionnaires, 6 (7.2%) of the 83 patients with Sturge-Weber syndrome and brain involvement reported maternal hypothyroidism. One additional patient reported maternal hyperthyroidism, and one reported positive anti-thyroid antibodies.

Subject 1

A 9-year, 8-month-old girl with a right-sided facial port-wine stain from birth was diagnosed with Sturge-Weber syndrome at age 6 years. She was healthy and developing normally until age 6 years, when she manifested an episode of left-sided weakness, leading to hospitalization. Computed tomography of the head revealed right-sided brain calcifications, consistent with Sturge-Weber syndrome. Postcontrast magnetic resonance imaging of the brain indicated diffuse enhancement and thickening of the leptomeninges over the right parietal, occipital, and temporal lobes (**Fig 1**). She exhibited normal results on waking and sleeping electroencephalogram a few months later, with no epileptiform discharges or lateralizing signs. During hospitalization, she manifested several seizures and severe headaches as well as pneumonia. She began oxcarbazepine therapy and low-dose aspirin and topiramate were initiated soon thereafter. She had also been diagnosed with right-eye glaucoma, for which she uses dorzolamide hydrochloride-timolol maleate eye drops daily. Her family history was significant for hypo-

thyroidism in both her maternal grandmother and paternal grandmother.

At age 8 years, the patient continued to manifest seizures, and these had increased in frequency in the past several months. She also complained of recent significant fatigue, weight gain, and both skin and hair changes which included dry skin, hair, and scalp over the past year, and an excessive loss of hair with brushing. She reported both heat and cold intolerance. She was overweight (>99th percentile) and of average height (50th percentile). She also complained of frequent headaches. She had been doing well in school until that year, when her grades worsened. Thyroid function tests were performed, and revealed free thyroxine at 0.62 ng/dL (normal range, 0.7-1.6 ng/dL); total free thyroxine at 4.5 µg/dL (normal range, 5.5-11.0 µg/dL); thyroid-stimulating hormone (thyroid-stimulating hormone) at 2.69 µIU/ml (normal range, 0.47-4.68 µIU/ml). The results for anti-thyroglobulin and anti-thyroid peroxidase antibodies were negative. The results of her laboratory studies were consistent with central hypothyroidism. After a normal morning cortisol was documented, she was started on levothyroxine 25 µg daily, and the results of her thyroid tests returned to normal. Although her growth velocity was normal, her

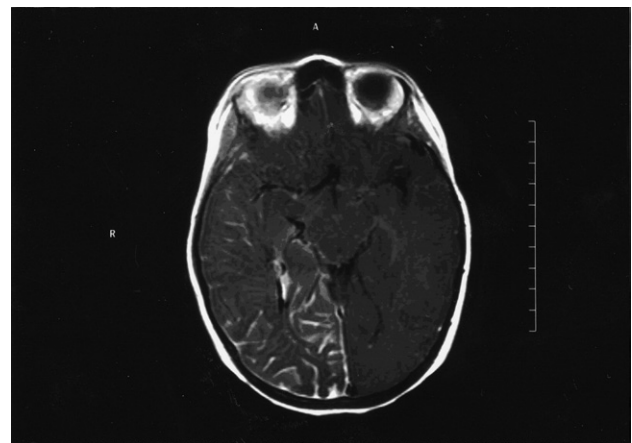


Figure 1. T_1 -weighted postcontrast axial magnetic resonance image (TR/TE = 480/14 ms) of subject 1, indicating diffuse enhancement and thickening of the leptomeninges over the right parietal, occipital, and temporal lobes. Right occipital atrophy and enhancement in the right choroid plexus are also demonstrated.

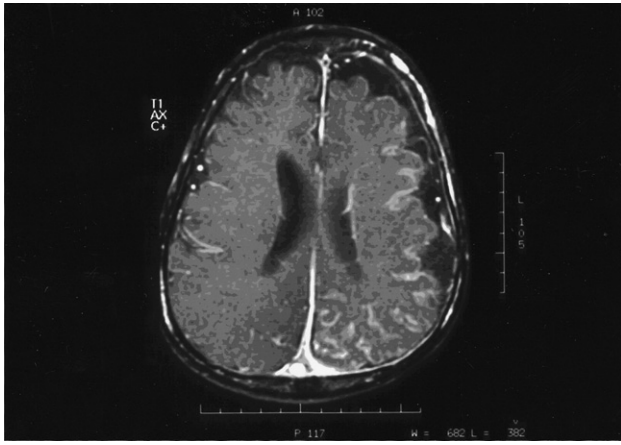


Figure 2. T_1 -weighted postcontrast axial magnetic resonance image (TR/TE = 666/20 ms) of the brain of subject 2 at age 7.5 years, indicating left-hemispheric involvement. Significant atrophy of the left hemisphere is evident, along with extensive leptomeningeal enhancement over the entire left cortical surface.

level of insulin-like growth factor-1 was 68 ng/mL (normal range, 110-565 ng/mL). Growth hormone stimulation testing is planned if there is a future deceleration in her growth velocity.

Several months after the initiation of levothyroxine replacement, her free thyroxine returned to a normal level, at 0.62 ng/dL (normal range, 0.58-1.64 ng/dL), the patient became seizure-free, and her skin and energy issues improved, as did her hair loss. The headaches also improved, becoming infrequent and typically resolving without medication. She has had no recurrence of stroke-like episodes, and her left-sided weakness resolved completely.

Subject 2

A 12-year-old left-handed boy with Sturge Weber syndrome and a port-wine stain on the left side of his face, right arm, and upper back presented at our center for evaluation. According to parental history, he did well in the newborn period, but lost his motor and language skills at 13 months of age and at 8 years of age, when he manifested stroke-like episodes. His first seizure occurred at age 8 months, and he was given phenobarbital. Complex partial seizures recurred at age 13 months, involving the right side with stroke-like events. Over the next several years, he manifested intermittent seizures, and several anticonvulsant combinations were tried. He had gross and fine motor impairments and learning difficulties, and was not completely toilet-trained until age 5 years. Magnetic resonance imaging of the brain at 7 years and 6 months of age revealed typical left-sided brain involvement (Fig 2). A positron emission tomography scan, however, also revealed diffuse left-cortical hypometabolism and hypometabolism in the right sensory motor cortex. An electroencephalogram indicated discharges over the left temporal and frontal regions. A vagal nerve stimulator was implanted, and the family used the magnet successfully to

abort seizures. The family history was significant for hypothyroidism in the maternal grandmother.

The patient presented with right-sided hemiparesis, an intelligence quotient below normal (verbal intelligence quotient, 51; full-scale score, 47; and nonverbal intelligence quotient, 48), and left-eye glaucoma. He continued to manifest 2-4 seizures per month, lasting 1-2 minutes and consisting of staring, drooling, and posturing of his right hand. His medications included oxcarbazepine and low-dose aspirin. Thyroid function tests revealed a thyroid-stimulating hormone level of 1.15 μ IU/mL (normal range, 0.50-4.50 μ IU/mL), and a free thyroxine level of 0.6 ng/mL (normal range, 0.7-1.6 ng/mL). His anti-thyroid antibodies revealed no evidence of autoimmune thyroid disease. In addition, his growth velocity was decelerating.

These laboratory tests were repeated soon afterward, and produced similar results, with a low level of free thyroxine and a normal level of thyroid-stimulating hormone. After documentation of a normal level of morning cortisol, levothyroxine therapy was initiated, and a few months later his level of free thyroxine returned to normal (at 0.8 ng/dL). The frequency and severity of his seizures, however, were unchanged. Cognitively, he was more verbally interactive, although his behavior worsened, as is frequently observed when hypothyroidism is corrected. He will be evaluated for possible growth-hormone deficiency in light of a recent linear growth deceleration.

Discussion

Central hypothyroidism is a rare condition, with a prevalence of 0.0002-0.005% in the general population, which arises from inadequate release of thyroid-stimulating hormone to stimulate an otherwise normal thyroid gland [4]. Central hypothyroidism is often associated with a deficient secretion of other pituitary hormones, and idiopathic isolated central hypothyroidism remains extremely rare [5]. In our population of 83 patients with Sturge-Weber syndrome and brain involvement, we found 2 cases with central hypothyroidism out of 83 patients with Sturge-Weber syndrome, which is a prevalence of 2.4%, or approximately 500-10,000 times the prevalence in the general population [4]. An important limitation of this study, however, is that most of the patients seen at our center over this period did not undergo thyroid-function tests, making our reported prevalence of central hypothyroidism in Sturge-Weber syndrome likely to be falsely low. We only recently initiated this screening as part of our routine care for Sturge-Weber syndrome. Our euthyroid patients also generally receive carbamazepine or oxcarbazepine; these are our first-choice anticonvulsants for most patients with Sturge-Weber syndrome.

One possible reason for the central hypothyroidism in these children is their use of anticonvulsants [6-9]. Both subjects had been receiving anticonvulsants chronically (oxcarbazepine and topiramate). Subject 1 was also clinically symptomatic, with weight, hair, skin, and behavior

changes consistent with clinical hypothyroidism. Subject 2 was diagnosed as the result of a routine check of thyroid function. Subject 1 manifested definite improvement in her weight, hair, skin, and fatigability in response to levothyroxine treatment, and that improvement corresponded with control of her seizures. In subject 2, the response was less clear-cut, although he experienced a subjective increase in his activity level and interactiveness. According to a recent follow-up of this family, they are very happy with the unexpected progress being made in school since the initiation of Synthroid. They are unwilling to stop the levothyroxine therapy because of this progress. His refractory seizures were not altered by the levothyroxine treatment.

Central hypothyroidism was recently reported in 3 patients on oxcarbazepine: 2 patients manifested lethargy, weight gain, and dry hair, and one presented with a poor linear growth velocity [9]. Improvement of these signs occurred during levothyroxine therapy. We did not find any association in the literature between topiramate and central hypothyroidism. There is, however, one case of undefined hypothyroidism and topiramate. That patient was also receiving valproic acid, and thus the link with topiramate is uncertain [10]. The euthyroid patients we tested were not taking noninducing AEDs. Our first-choice anticonvulsant in Sturge-Weber syndrome is oxcarbazepine (or alternatively, carbamazepine). Most of the euthyroid patients were also receiving these AEDs. Therefore, if anticonvulsants played a role in the central hypothyroidism that developed in these 2 patients, they are probably not the only contributing factor.

However, it is crucial to keep in mind that patients with Sturge-Weber syndrome have an increased prevalence of growth-hormone deficiency, thereby making the disruption of the hypothalamic-pituitary axis by Sturge-Weber syndrome itself a suspect in the etiology of the central hypothyroidism. Hence, the pituitary axis must be evaluated if there are any suggestive clinical signs. Central hypothyroidism was also reported in association with the posterior fossa abnormalities, hemangioma, arterial anomalies, cardiac defects, eye abnormalities, and sternal clefting association, another vascular birthmark associated with congenital intracranial vascular and nonvascular malformative abnormalities [11]. A difficult aspect of central hypothyroidism in the setting of Sturge-Weber syndrome is that some of its signs (e.g., inattention, sleepiness, obesity, headaches, and behavioral issues) could result from any of the following factors: central hypothyroidism, anticonvulsants, seizures, Sturge-Weber syndrome-related brain injury, and behavioral problems. Thus, in subject 1, the need to test for hypothyroidism was obvious, but in many cases, the need to test is likely to be much less apparent. We did not find reports in the literature of hypothyroidism increasing seizures.

Topiramate-associated glaucoma is very rare in children. In addition, the mechanism for topiramate-associated glaucoma is very different from the pathology causing

glaucoma in Sturge-Weber syndrome. Therefore, it is not thought likely that topiramate will exacerbate Sturge-Weber syndrome-related glaucoma. Furthermore, these children are monitored for eye pressure much more closely than other children on topiramate for their epilepsy. In our clinical experience, topiramate precipitating glaucoma has not been an issue. Brain atrophy and calcification in Sturge-Weber syndrome can worsen over time, and may be associated with stroke-like episodes, the onset or worsening of hemiparesis, visual field cut, or cognitive impairment [12]. Because this injury is thought to be secondary to impaired blood flow to the involved areas, as revealed by single-photon emission computed tomography and perfusion imaging, low-dose aspirin has been used to decrease stroke-like episodes and neurologic injury [13], although the proof of aspirin's effectiveness for Sturge-Weber syndrome is still lacking.

Our approach is to test thyroid-stimulating hormone and free thyroxine in any patient with Sturge-Weber syndrome for any of the aforementioned problems or for uncontrolled seizures, stroke-like episodes, or signs of hypothyroidism. The diagnosis of central hypothyroidism must be based on normal or low levels of thyroid-stimulating hormone and low free thyroxine, because thyrotropin-releasing hormone, which was used in the past, is no longer available. If there is evidence of central hypothyroidism in Sturge-Weber syndrome, it is clinically important to evaluate the other hormones of the hypothalamic-pituitary axis, because the presence of one central hormonal deficiency can be associated with other hormonal problems.

It is very difficult to distinguish between central hypothyroidism secondary to anticonvulsants and central hypothyroidism attributable to hypothalamic-pituitary dysfunction. Clearly, if a patient could be weaned from anticonvulsant treatment, it would be possible to determine whether thyroid function improved after a brief period of discontinuation of thyroid hormone replacement as well. Conversely, if a patient exhibited or developed other concomitant central hormonal deficiencies, a central etiology of the hypothyroidism would be most likely.

Our recommendation is that if the level of free thyroxine is consistently low, then these patients should be started on levothyroxine, but only if there are normal morning cortisol levels. Treatment with levothyroxine in the face of cortisol deficiency could lead to adrenal insufficiency secondary to increased clearance of cortisol by thyroxine replacement [8], and cortisol levels need to be determined as normal before initiation of levothyroxine in all cases of central hypothyroidism. Brain imaging studies, which are part of the routine standard of care in patients with Sturge-Weber syndrome because of neurologic abnormalities, should specifically evaluate the hypothalamic-pituitary region as part of the analyses.

If the level of free thyroxine is not consistently low, then we follow the patients frequently, especially young children in whom thyroxine is necessary for cognitive development [14]. Additional studies and long-term fol-

low-up are necessary to determine the long-term benefits or consequences of central hypothyroidism, its treatment, and a full understanding of its relationship to Sturge-Weber syndrome.

One of the authors (A.C.) reported that the expression of type 2 deiodinase II messenger RNA in the cortex of subjects with Sturge-Weber syndrome was decreased (as measured by microarray analysis and reverse transcription-polymerase chain reaction, and compared with control subjects with epilepsy) [15]. It is unclear whether this decreased expression is compensatory or pathologic. However, this observation suggests that the cortex of patients with Sturge-Weber syndrome is uniquely susceptible to low circulating thyroid hormone, because type 2 deiodinase is the enzyme that converts inactive thyroid hormone to active thyroid hormone within the astrocytes of the brain, for use by local neurons [16].

Our database search revealed that 7% of patients with diagnosed Sturge-Weber syndrome and brain involvement reported maternal hypothyroidism. The type of maternal hypothyroidism is not known in these data. The prevalence of hypothyroidism in the general population of women ranges between 1-12%. Therefore, our limited data do not support a role for maternal hypothyroidism as a risk factor for Sturge-Weber syndrome.

In conclusion, central hypothyroidism is more common in Sturge-Weber syndrome than in the general population. Although this central hypothyroidism could be secondary to anticonvulsant therapy, it is important to consider that it could also be secondary to hypothalamic-pituitary insufficiency, given that we know these patients have an increased prevalence of growth-hormone deficiency. Therefore, further hormonal workups for central hormonal deficiencies need to be considered. Levothyroxine therapy for central hypothyroidism should not be initiated until cortisol sufficiency is documented.

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