SHORT REPORT

Growth hormone deficiency in Sturge–Weber syndrome

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Sturge–Weber syndrome (SWS) is a disorder involving central nervous system abnormalities that may increase the risk of hypothalamic–pituitary dysfunction. Records of 19 patients with suspected growth hormone deficiency (GHD), identified from a registry of 1653 patients with SWS, were reviewed; nine patients with GHD were found.

Sturge–Weber syndrome (SWS) is a neurocutaneous disorder characterised by glaucoma, leptomeningeal angiomas, and vascular malformations of the skin. The underlying parenchyma may be atrophic, with multiple calcified granular deposits.[1]

There are only isolated case reports describing endocrine abnormalities associated with this condition.[2–4] One would suspect the hypothalamic–pituitary axis would be at risk for impairment given the abnormalities that often occur in SWS. The growth hormone (GH) secreting cells of the pituitary are particularly sensitive to vascular insult and may have increased risk of damage in SWS.

We conducted a retrospective chart review of children with SWS and suspected GH deficiency (GHD). We report the findings of nine children with SWS found to have GHD.

SUBJECTS AND METHODS

Approval for this study was received from the Johns Hopkins Medical Institutions Institutional Review Board. We reviewed files in a registry maintained by the Sturge–Weber Foundation for which all data was provided by parents and patients on a voluntary basis. Medical records were obtained for 19 patients with suspected GH deficiency (with identifiers removed).

Of the 19 patients, four did not respond to requests for records. Of the remaining 15 patients, one had no identifiable endocrine complaint, four were referred to an endocrinologist for concerns other than growth, and 10 had evidence of GHD. We were unable to obtain test results confirming GHD in one of the 10 patients; this subject was not included in our analysis.

Testing for GHD and other endocrine diagnoses was performed according to each institution's protocol. Information on the specific assay used for each patient was not available. For the purposes of this report, a GH stimulation test was considered abnormal if the peak GH level was $\leqslant 7$ μg/l, as this is the strictest criterion for GHD in children.

RESULTS

Eight of nine patients with GHD were male with age at diagnosis 3.6 years to 19 years. *x* Ray examination revealed delayed bone age in all patients, with a mean delay in bone age at time of diagnosis of 1.7 years. All patients had an IGF-1 level below normal limits for Tanner stage. All patients had a height more than 1.5 standard deviations (SD) below mean height for age, with an average of 2.8 SD below the mean, and six of seven patients had significantly abnormal growth velocities (table 1).

GHD was verified with data from formal GH stimulation testing with one or two agents, as indicated. All subjects had subnormal peak GH levels on provocative testing with normal thyroid hormone levels at the time of GH testing. Information on priming with sex steroid is not available (table 2).

Patients were started on GH at doses ranging from 0.2 to 0.3 mg/kg/wk. Mean growth velocity was 3.4 cm/y prior to treatment and 9.5 cm/y over the first year of treatment. The seven patients with adequate follow up data (patients 2–8) had improvement in height SD following GH treatment, with five patients at or near adult stature at the time of last measurement (patients 3, 5, 6, 7, 8) (table 2).

Table 1 Characteristics of nine patients with SWS and GHD

Patient no.	Sex	Mid-parental height (SD)	Age at presentation (y)	Tanner stage (I–V)*	BMI (kg/m^2)	Height at presentation (SD)	Pretreatment GV (cm/y)	Bone age prior to treatment (y)
1	M	−0.55	19	I	33.5	−6.97	0	CA = 20 BA = 13
2	M	N/A	3.8	I	15	−2.42	4.2	CA = 5.3 BA = 3.5
3	F	0.47	11.8	III	28.7	−1.57	6	CA = 11.5 BA = 8.8
4	M	−0.8	11.9	I	18.2	−3.17	5.4	CA = 11.9 BA = 11
5	M	N/A	15.2	N/A	21.4	−2.52	N/A	N/A
6	M	N/A	15.4	II	29.2	−1.54	N/A	CA = 15.5 BA = 14
7	M	0.86	15.6	II	28.1	−2.82	8	N/A
8	M	−0.57	12.3	II	26.2	−2.01	2.9	CA = 12.25 BA = 12.5
9	M	N/A	5.2	I	N/A	−1.87	5	CA = 6.7 BA = 5

N/A, data not available; CA, chronological age; BA, bone age; GV, growth velocity.
*Staging by breast development for girls, genital development for boys (Tanner JM. *Arch Dis Child* 1976;**51**:170–9).

Table 2 Results of testing and response to treatment

Patient no.	IGF-1 (nMol/l)*	Peak GH (stimulation testing, µg/l)	Other endocrine testing	Last measured height (SD)	Last bone age (y)
1	8.6 (14–63)	1.2 (arginine, l-dopa)	TSH 0.83 mU/l, unbound T4 13.4 pMol/l†, LH 0.2 IU/l, FSH 0.69 IU/l, testosterone <0.1 nMol/l	No change‡	CA = 21 BA = 13.5
2	5.9 (14–63)	6.2 (clonidine), 4.7 (l-dopa)	TSH 3.04 mU/l, unbound T4 14.2 pMol/l, cortisol 201 nMol/l, IGFBP-3 0.9 mg/l	−1.75 at 6.6 y	N/A
3	11.7 (38–115)	<1.5 (arginine, clonidine)	TSH 3.46 mU/l, cortisol 453 nMol/l	−0.33 at 16 y	CA = 12 BA = 10
4	1.6 (14–63)	3.9 (clonidine)	TSH 4.0 mU/l, unbound T4 16.7 pMol/l	−1.12 at 15.8 y	CA = 15.8 BA = 14.25
5	6.5 (26–124)	0.3 (insulin), <0.1 (clonidine)	TSH 1.7 mU/l, cortisol 938 nMol/l	−0.8 at 17.3 y	N/A
6	17.0 (23–67)	1.3 (clonidine), 1.0 (insulin)	TSH 4.0 mU/l, T4 109 nMol/l, cortisol 646 nMol/l, LH 9.2 IU/l, FSH 7.1 IU/l§	0.34 at 18 y	CA = 18.1 BA = 17
7	7.7 (23–67)	0.5 (insulin, arginine)	TSH 0.93 mU/l, cortisol 168 nMol/l, ACTH 7.5 pMol/l	0.25 at 18 y	CA = 17.5 BA = 15
8	6.5 (23–67)	0.9 (l-dopa), 0.6 (clonidine)	TSH 0.97 mU/l, T4 76 nMol/l, cortisol 221 nMol/l	−1.47 at 19 y	CA = 17.1 BA = 15
9	N/A	3.8 (insulin)	N/A	N/A	N/A

N/A, data not available; IGF-1, insulin-like growth factor 1.
*Reference ranges for IGF-1 are provided according to Tanner stage.
†On levothyroxine.
‡Patient has just started GH.
§GnRH stimulated testing.

Brain MRI or head CT reports were available for eight of the nine subjects with GH deficiency. There were no pituitary abnormalities documented in any of the studies. However, small optic nerves were noted in the MRI report of subject 9.

Several patients with GH deficiency were also found to have other central hormonal abnormalities. Patient 1 had no evidence of puberty at age 20 despite a bone age of 13 years, with biochemical results suggestive of central gonadotropin deficiency. Patient 3 had onset of breast development at age 9, but had not undergone menarche by age 16. Records of her work-up for amenorrhea are not available. Patient 7 was diagnosed with partial ACTH deficiency after measurement of cortisol levels following hypoglycaemia revealed a peak of 334 nMol/l.

DISCUSSION

In the current medical literature, there are two reports of SWS affecting the hypothalamic–pituitary axis.[3 4] Here we present the first case series of patients with SWS and GHD. In the present study, nine patients out of a registry of 1653 people with SWS met clinical and laboratory criteria largely suggestive of GHD, a prevalence of approximately 0.54%. This is 18-fold higher than the general population prevalence of GH deficiency of approximately 0.03%.[5]

As with any retrospective study, there are limitations to interpreting the prevalence of GHD in our investigation. There may be children with SWS who have undiagnosed GHD, with their short stature or growth failure attributed to their chronic disease. Alternatively, the rate of detection of GHD in SWS may be higher, due to more frequent visits to physicians than the general population.

There are several other considerations in children with SWS when considering the diagnosis of GHD. First, the aetiology of GH deficiency in SWS is unclear. In our case review, no patients had obvious involvement of the pituitary gland on imaging studies. Structural abnormalities may be present but not identified by MRI. One also needs to consider a neurosecretory defect as the cause of growth failure. These patients may have normal pituitaries but functional GH deficiency due to injury to the hypothalamus.

The present study highlights the importance of considering GH deficiency as the aetiology of short stature or impaired growth velocity in children with SWS. More research needs to be done in order to determine accurately the prevalence of GH deficiency in SWS and to determine whether there are other associated endocrine disorders that also occur more frequently in SWS.

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