Diencephalic Syndrome: A Cause of Failure to Thrive and a Model of Partial Growth Hormone Resistance

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ABSTRACT. Diencephalic syndrome is a rare but potentially lethal cause of failure to thrive in infants and young children. The diencephalic syndrome includes clinical characteristics of severe emaciation, normal linear growth, and normal or precocious intellectual development in association with central nervous system tumors. Our group initially described a series of 9 patients with diencephalic syndrome and found a reduced prevalence of emesis, hyperalertness, or hyperactivity compared with previous reports. Also, the tumors were found to be larger, occur at a younger age, and behave more aggressively than similarly located tumors without diencephalic syndrome. We have been able to extend our follow-up of the original patients, as well as describe 2 additional cases. Because the mechanism of the growth and endocrinologic findings in diencephalic syndrome has not been explained, we report on these patients in light of current research on hypothalamic factors that affect growth and weight. This study emphasizes diencephalic syndrome as a model for additional study of growth hormone resistance and metabolic regulation of adiposity. *Pediatrics* 2005;115:e742–e748. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2237; *brain tumors, failure to thrive, growth hormone, growth patterns.*

ABBREVIATIONS. CNS, central nervous system; GH, growth hormone; RIA, radioimmunoassay; IRMA, immunoradiometric assay; IGF-I, insulin-like growth factor-I; SDS, SD score.

In 1951, Russell[1] described the clinical entity of diencephalic syndrome as profound emaciation in infancy with the absence of subcutaneous adipose tissue, despite normal or slightly diminished caloric intake. Linear growth was maintained. Other features included locomotor overactivity, hyperalertness, hyperkinesis, and euphoria. An association was noted with neoplasms of the anterior hypothalamus. In 1972, Addy and Hudson[2] reported on a series of 3 children and reviewed the literature to summarize a total of 48 similar cases, including the 12 described by Russell. Since then, several case studies have been reported with similar symptoms, a few with brain tumors located in the posterior fossa.[2,3] Nystagmus and vomiting were also noted in the majority of reported cases.[2–5] In 1976, a review of 72 cases by Burr[6] confirmed the clinical characteristics of diencephalic syndrome. Subsequent literature has consisted of multiple case series and case reports of this syndrome.

We reviewed the 11 cases of diencephalic syndrome that presented to Children's Hospital Boston and Dana-Farber Cancer Institute between 1970 and 2003. Our group initially described a series of 9 patients with diencephalic syndrome and found a reduced prevalence of emesis, hyperalertness, or hyperactivity compared with previous reports.[7] Also, the tumors were found to be larger, occur at a younger age, and behave more aggressively than similarly located tumors without diencephalic syndrome. We have been able to extend our follow-up of the original patients, as well as describe 2 additional cases. In our series, hyperemesis, hyperkinesis, and nystagmus were only rarely identified despite the classic presentation of emaciation, normal linear growth, and central nervous system (CNS) neoplasms. Thus, CNS tumors must be considered in any child who presents with severe, unexplained failure to thrive with preservation of linear growth rate. This specific form of failure to thrive occurs in the setting of elevated growth hormone (GH), suggesting a model of acquired partial GH resistance, as well as abnormalities in other related pathways.

METHODS

To characterize the population of patients with diencephalic syndrome, we performed a retrospective review of the clinical records of patients who received a diagnosis of diencephalic syndrome at Children's Hospital Boston and Dana-Farber Cancer Institute between 1970 and 2003. The Institutional Review Boards of both institutions approved the study. Eleven patients met criteria for diencephalic syndrome with hypothalamic neoplasms and failure to thrive in the setting of normal developmental milestones and continued age-appropriate linear growth. All patients had initially been brought to medical attention for failure to gain weight appropriately and were subsequently found to have CNS tumors. None of the patients had neurofibromatosis type 1.

Some endocrine evaluation was performed for all of the patients. All assays were performed at the Children's Hospital Boston endocrine laboratory, except where specified. Children's Hospital Boston has used various hormone assays over the 34-year study period. GH was assayed by radioimmunoassay (RIA) until 1987; by immunoradiometric assay (IRMA; Nichols Institute, San

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Accepted for publication Dec 16, 2004.
doi:10.1542/peds.2004-2237
No conflict of interest declared.

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Juan Capistrano, CA) until July 1, 1995; and by DELFIA (Perkin Elmer, Perkins Institute, Norwalk, CT), a fluorometric assay method, and then Auto DELFIA between July 1, 1995 and October 31, 1996. The Nichols IRMA was used again until 1999, when the Nichols Advantage Analyzer replaced it. Cortisol was assayed by RIA until May 1, 1994, by DELFIA until May 8, 1996, and by an immunoassay (Bayer Diagnostics, Tarrytown, NY) since May 9, 1996. Insulin-like growth factor-I (IGF-1) was sent to Endocrine Sciences until July, 1988, then measured by the Children's Hospital Boston endocrine laboratory by RIA (Nichols Institute) until 1999, followed by the Nichols Advantage Analyzer to present. Thyrotropin was assayed by IRMA (Nichols Institute). Thyroxine was assayed by RIA (Nichols Institute) until 1991, by DELFIA until 1996, and by immunoassay until the present. Growth data were analyzed according to the Centers for Disease Control and Prevention 2000 standards using STAT GrowthCharts, Version 2.0 (www.statcoder.com) to calculate percentiles and SD scores (SDS).

RESULTS

Between 1970 and 2003, 11 children presented to Children's Hospital Boston and the Dana-Farber Cancer Institute with extreme failure to thrive and were found to have CNS neoplasms. This group consisted of 5 girls and 6 boys.

The median age at diagnosis was 18 months (range: 4–56 months; mean: 23 months). The duration of failure to thrive as defined by minimal or no weight gain was a mean of 12.5 months (range: 2–33 months). Two of the patients had previously received a diagnosis of reflux as a cause for their failure to thrive. One patient had been treated for celiac disease, and 1 was assumed to have lipodystrophy. Previous alternative diagnoses were not correlated with a longer duration of symptoms before discovery of the CNS neoplasm and confirmation of diencephalic syndrome.

Original reports of the diencephalic syndrome described characteristic locomotor hyperactivity. However, in the 11 patients in our study, hyperkinesis was reported in only 1 (9%), whereas 3 patients (27%) were actually described as lethargic by caregivers. The 3 lethargic patients did have mild to moderate hydrocephalus at presentation (see below), but the degree of hydrocephalus was not believed to be significant enough to account for an altered level of alertness or activity. Seven (64%) of the 11 patients were characterized as particularly happy and social children. All were noted to have met developmental milestones before or at age-appropriate times.

Persistent emesis has been reported as a common presenting symptom of diencephalic syndrome.[6] However, vomiting was present in only 4 (36%) of 11 in our case series. Hydrocephalus or enlarged ventricular size was noted in 6 (55%) of 11 of our patients, similar to previously published reports of 33% to 58%.[4,8] Only 1 of the 4 patients with vomiting had hydrocephalus on the initial imaging study. Therefore, the presence of vomiting was not explained by an increase in intracranial pressure at the time of diagnosis in the majority of patients.

Earlier case series found nystagmus to be a common presenting symptom in diencephalic syndrome. In our series, nystagmus was present in only 3 patients. One of these 3 patients had papilledema at presentation. This patient was also 1 of the 6 patients who had hydrocephalus on neuroimaging. The other 8 (73%) patients had normal ophthalmologic evaluations. The 3 patients with nystagmus at presentation and 1 of the other patients eventually progressed to have significant visual loss. Two of these 4 patients were evaluated with full dilated ophthalmologic evaluation and found to have mild optic pallor, 1 at presentation and 1 at a later evaluation.

At presentation, 10 of the 11 patients had weights >2 SD below the mean for age (mean: −2.8; range: −0.73 to −3.89), and the 1 patient who was not significantly underweight (SDS: −0.73) was significantly underweight for height (SDS: −2.41). The weight-for-height measurements were >2 SD below the mean for age in all 11 patients studied (SDS range: −2.41 to −8.72). The heights at diagnosis all were within normal range for age (range: 10% to 97%; SDS: −1.27 to 1.90). Five (45%) of the 11 patients were above the mean for age in height (Table 1). Figure 1 shows examples of growth charts in 2 of these patients, demonstrating a relatively preserved linear growth rate in the setting of poor weight gain or weight loss. Of note, patient B, who had dramatic weight loss, eventually had some slowing of her growth rate.

Some endocrinologic evaluation was pursued in all patients before initiation of therapy for the intracranial neoplasm. Thyroid hormone levels were within normal limits in all 11 patients. Despite that random GH levels are often low because GH is secreted in a pulsatile manner,[9] 3 patients had high normal to mildly elevated levels (3.3, 4.6, and 5.4 ng/mL; normal range: 0.0–4.0 ng/mL), whereas 6 patients had significantly elevated levels (range: 12.7–134.4 ng/mL). One elevated value was obtained after initial surgical biopsy. None of the 4 patients tested had appropriate suppression of GH after an oral glucose load. IGF-1 concentrations were found

TABLE 1. Auxologic Data at Time of Diagnosis

Patient	Length, %	Length, SDS	Weight, %	Weight, SDS	Weight-for-Length, SDS
1	97	1.90	2	−1.93	−4.57
2	23	−0.70	<1	−3.42	−4.08
3	13	−1.08	<1	−2.33	−2.69
4	10	−1.27	<1	−2.85	−3.31
5	57	0.29	<1	−3.50	−5.41
6	75	0.68	1	−2.61	−3.33
7	82	0.94	23	−0.73	−2.41
8	57	0.30	<1	−3.52	−8.72
9	49	−0.01	1	−2.71	−3.98
10	35	−0.38	<1	−2.95	−3.62
11	11	−1.17	<1	−3.89	−3.95

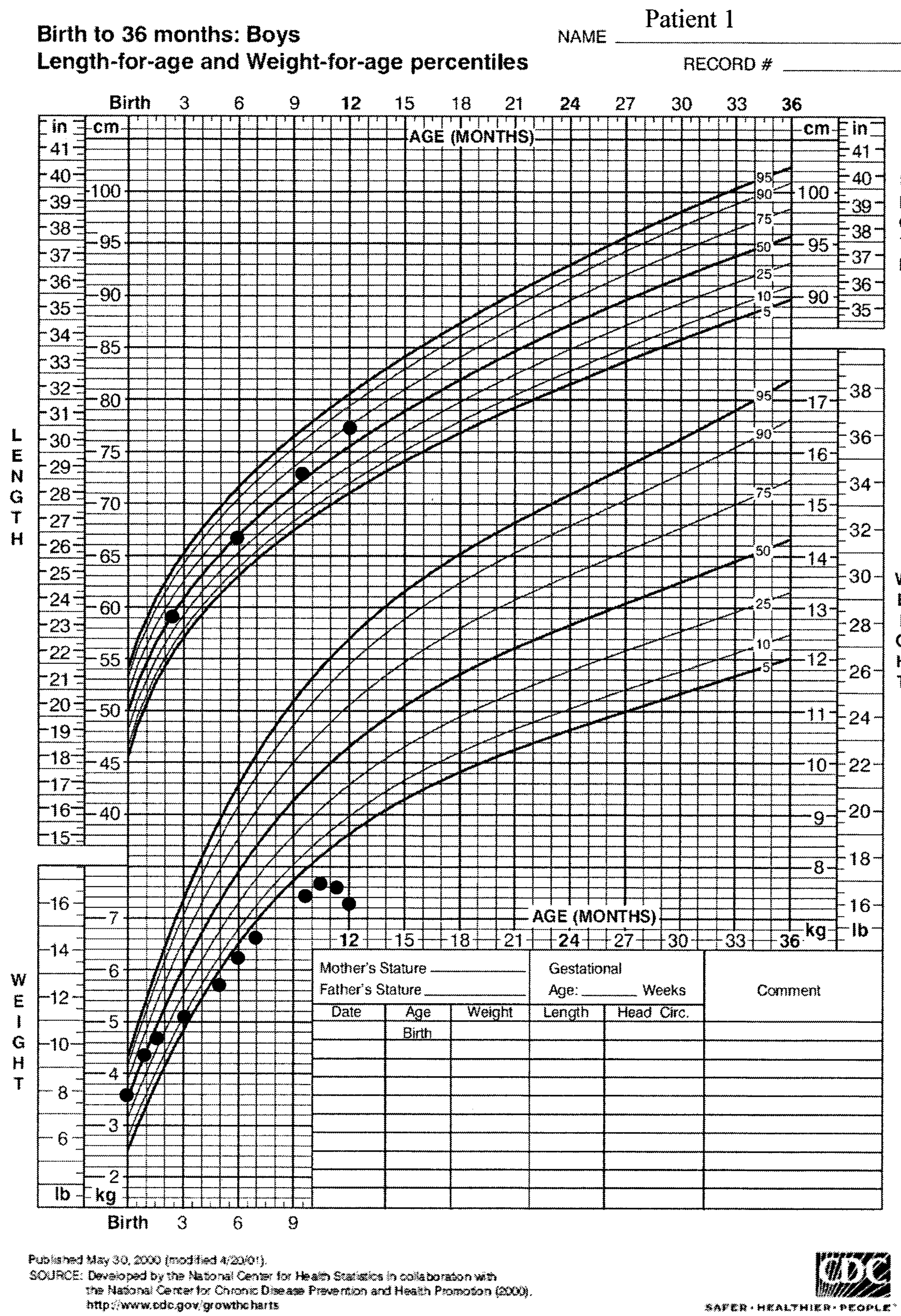

Fig 1. Growth charts at presentation. Auxologic data from birth to time of diagnosis in 2 patients with diencephalic syndrome.

within the normal range for age in all patients evaluated, with 4 of 7 patients having high-normal values (Table 2). Random cortisol levels were measured in 6 patients and found to be high-normal to elevated in 4 (67%) at 23 to 34.8 μg/dL (normal range: 5–25 μg/dL), in contrast to random values often being low because of the diurnal rhythm in cortisol secretion.[10,11]

Pathologic diagnosis was available in 8 cases. Four patients had pilocytic astrocytomas, and 4 had fibril-

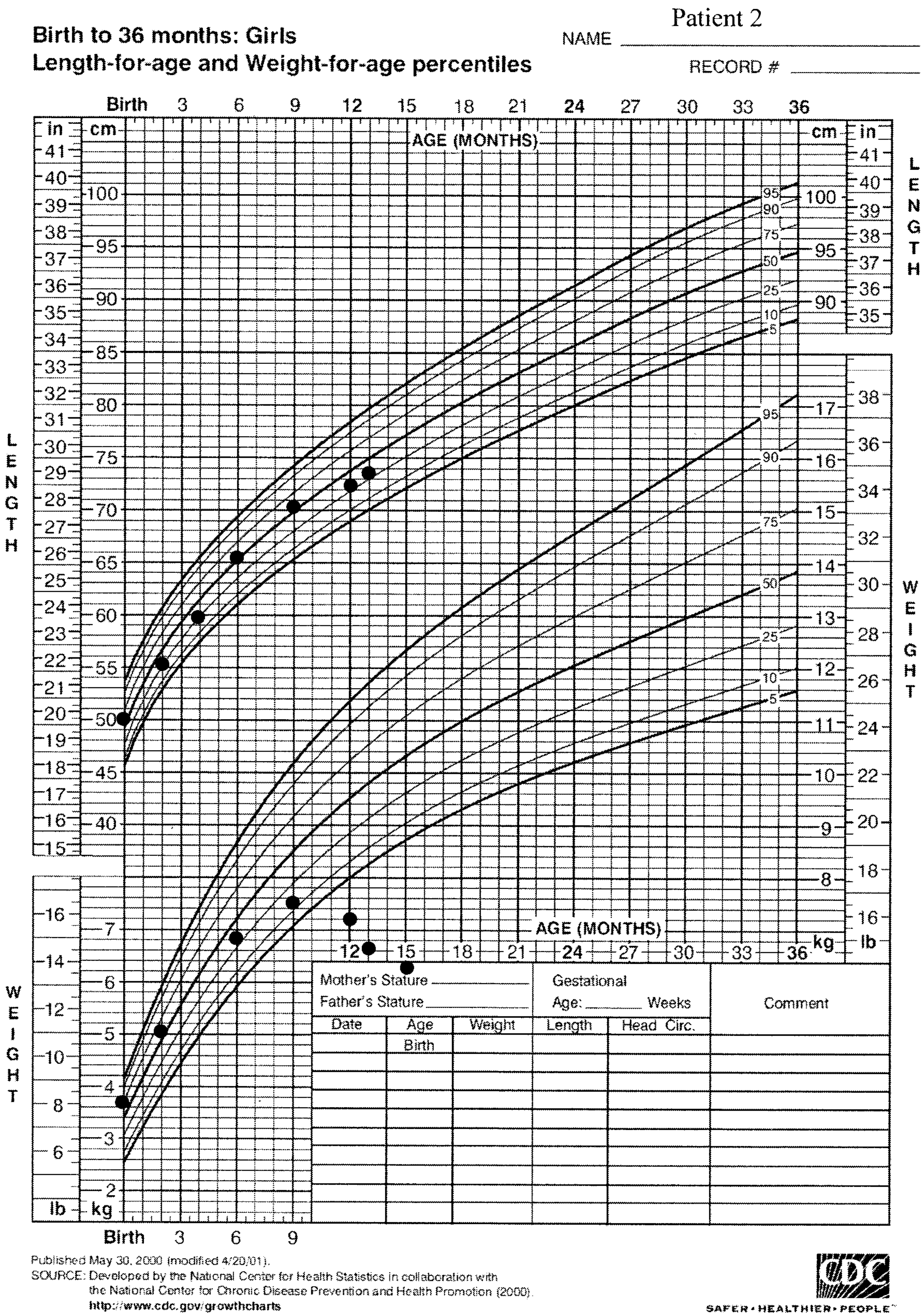

Fig 1. Continued.

lary astrocytomas (Table 3). Three of the 11 patients had spinal seeding identified at the time of presentation. Spinal metastases were discovered in 2 additional children during treatment, 20 months and 7.5 years after initial presentation. Neither of these 2 patients had spinal imaging at the time of diagnosis. All 3 of the children with spinal seeding noted at presentation eventually died from tumor progression despite therapy. Three of the children with local disease also died from progression of their tumors. The patients' ages at time of death ranged from 8 months to 13 years. The mortality rate in this series

TABLE 2. GH and IGF-1 Levels

Patient	Baseline GH Level, ng/mL	GH Response, ng/mL (Normal: <1)	IGF-1 Levels
1	4.6	—	—
2	>32	8.5	—
3	3.3	—	—
4	5.4	34	0.87 U/mL (normal: 0.15–2.3)
5	20.6	19	—
6	134.4	25	60 ng/mL (normal: 17–248)
7	35	—	112 ng/mL (normal: 17–248)
9	12.7	—	110 ng/mL (normal: 17–248)
11	15.4 (postoperatively)	—	39 ng/mL (normal: 17–248)

GH Response indicates the lowest level over a time period of 2 hours after an oral glucose load. Baseline GH levels are random if not performed with an oral glucose load and fasting if performed with an oral glucose load.
— indicates that the data were not available.

was 55% (6 of the 11 children), although 2 of the patients who are assumed to be living have been lost to follow-up.

Surgical interventions, chemotherapy, and radiation treatment varied on the basis of the location and the extent of tumor, as well as the year of diagnosis and current therapeutic standards. Seven patients had an initial subtotal resection or biopsy of the primary tumor site. One patient had only a biopsy of a spinal cord mass at the time of diagnosis. Six patients were treated with localized radiation and initially responded to therapy. Two were lost to follow-up, 2 died, and 2 are alive, 1 with tumor progression requiring additional treatment with chemotherapy. Four patients received chemotherapy as part of initial treatment protocols with vincristine and carboplatin, a current medical regimen. One patient has recently completed her initial course of therapy. The remaining 3 patients who were treated with chemotherapy died after disease progression despite receiving additional treatments. One young patient with a high-grade astrocytoma was considered terminal and received only comfort measures without chemotherapy or radiation (Table 3).

DISCUSSION

The literature on diencephalic syndrome consists of case reports and case series describing young children with emaciation, growth acceleration, hyperkinesis, and euphoria.[1–3,6] Vomiting was present in most of the cases. In addition, nystagmus with normal optic fundi, a flat fontanel, and the absence of other abnormal neurologic signs was noted in the majority of reports.[2,5,6] In this series of 11 patients with the classic presentation of emaciation, normal linear growth, and CNS neoplasm, hyperemesis, hyperkinesis, and nystagmus were not noted in the majority of patients. Hyperkinesis was observed in only 1 patient, whereas nystagmus was noted in 3 patients. Vomiting was described in 4 of the 11 patients. One can speculate that the accessibility of neuroimaging, particularly MRI, in the past 2 decades may have allowed for earlier diagnosis of this syndrome with fewer neurologic sequelae. However, Burr's[6] review of 72 cases in 1976 revealed a mean time from onset of symptoms to diagnosis of 7 months for anteriorly placed tumors. These patients' disease was diagnosed by skull and optic foramina plain radiograph films, cerebrospinal fluid analysis, and pneumoencephalography and subsequently confirmed by surgery in the majority of cases.[6] This average duration to diagnosis was shorter than the mean of 12.5 months (range: 2–33 months) in this case series.

The 11 patients described were brought to medical attention because of emaciation, rather than the visual impairment that often represents the first manifestation of hypothalamic and optic pathway gliomas not associated with diencephalic syndrome.[12] In a series of 46 children who had hypothalamic or optic pathway gliomas and were younger than 5 years, Janss et al[13] described the most common presenting sign as strabismus with decreased visual acuity on diagnostic evaluation. In our case series, no patients presented with visual complaints, but they may have been too young to verbalize a problem. However, on ophthalmologic examination, no one had decreased vision, although 3 patients had nystagmus and 1 of these patients had optic atrophy. Four of the 11 patients eventually developed visual deficits.

A 1997 study by Perilongo et al[14] indicated that of the 43 children who were evaluated at 1 institution with low-grade gliomas, including 12 patients with hypothalamic-optic chiasm gliomas, the 3 who presented with dissemination were the only 3 who had the clinical characteristics of diencephalic syndrome. This suggested an association between the diencephalic syndrome and early dissemination of gliomas. The general frequency of dissemination of low-grade gliomas is ~5%.[15] This low rate is partially explained by the benign nature of the low-grade optic gliomas that develop in neurofibromatosis type 1. None of our patients had neurofibromatosis. Of the 11 patients in our series, 3 had dissemination at diagnosis and 2 additional patients developed spinal metastases despite therapy. More than half of the patients described in this case series died from tumor progression, even in the era of modern treatment, suggesting that patients with early dissemination seem to have a poor prognosis despite aggressive therapy.

Multiple case reports and case series of diencephalic syndrome have confirmed an elevation in GH with a paradoxic response to a glucose load. In the past 3 decades, several papers have attempted to explain the abnormal GH secretion evident in these

TABLE 3. Treatment Course, Pathologic Diagnosis, and Outcomes

Patient	Surgery (Subtotal Resection or Biopsy)	Pathology	Spinal Metastases	Radiation, cGy	Chemotherapy	Second Resection	Additional Therapy	Survival
1	—	Not done	—	5000	—	—	—	Lost to follow-up
2	—	Not done	—	4600	—	—	—	Lost to follow-up
3	—	Not done	—	5300	—	—	—	Dead
4	Yes	Pilocytic astrocytoma	—	5760	—	—	—	Dead
5	Yes	Fibrillary astrocytoma	—	5400	—	Yes	VCR and CP, CCNU	Alive
6	Yes	Fibrillary astrocytoma	20 mo after diagnosis	—	VCR, CP	Yes	Radiation	Dead
7	Yes	Astrocytoma/oligo	7.5 y after diagnosis	5400			—	Alive
8	Yes	Pilocytic astrocytoma	At diagnosis	—	VCR, CP	Yes	PC, VCR, 6TG, CCNU, and radiation	Dead
9	Yes (spinal nodule)	High-grade astrocytoma (limited specimen)	At diagnosis	—	—	—	—	Dead
10	Yes	Pilocytic astrocytoma	At diagnosis	—	VCR, CP	Yes	—	Dead
11	Yes	Pilocytic astrocytoma	—	—	VCR, CP	—	—	Alive

— indicates that the data were not available; VCR, vincristine; CP, carboplatin; CCNU, lomustine; 6TG, 6-thioguanine.

patients. Pimstone et al[16] reported on 2 children with diencephalic syndrome and concluded that the cause of the loss of subcutaneous fat was unlikely to be completely explained by a decrease in intake or an increase in energy expenditure as a result of the variability of these features among patients. Our data reaffirm this variability, as decreased appetite and hyperkinesis were not characteristic of the majority of the patients studied. Because their patients had elevated GH levels with incomplete suppression after a glucose load, Pimstone et al suggested that a yet unspecified dysregulation of GH with subsequent mobilization of free fatty acids might explain the clinical findings. Drop et al[17] hypothesized that a lipolytic peptide, β-lipotropin, produced in excess by the tumor or secondary to invasion could explain the decrease in subcutaneous tissue and the excess GH release.

GH resistance has been found in individuals with anorexia nervosa, who have a similar degree of emaciation to that seen in diencephalic syndrome but secondary to extreme food restriction. Elevations in basal and pulsatile GH values, with suppressed levels of IGF-1, are found in this population.[18–20] The low IGF-1 levels are consistent with a peripheral GH resistance and decreased central feedback on the elevated GH release. Studies have indicated that the use of recombinant IGF-1 can suppress the GH release to some degree but does not normalize growth hormone releasing hormone–induced GH release.[21] Therefore, there are other factors involved in the dysregulated signaling of GH release in anorexia nervosa.

The normal IGF-1 levels and consistent linear growth in diencephalic syndrome suggest a more selective GH-resistant state than in anorexia nervosa and other forms of emaciation. The consistent finding of maintenance of linear growth also differentiates this diagnosis from that of other chronic illnesses or oncologic processes. Given the combination of normal or less effected linear growth in the setting of severe emaciation, it is likely that there are central factors that modify fat distribution without altering growth velocity. It is clear that such regulators would be valuable in the ongoing battle against the obesity epidemic.

Candidate factors for aberrant GH release in anorexia nervosa include somatostatin dysregulation[22] and hypercortisolemia.[23] The elevated random cortisol levels in the majority of our case series suggests that hypercortisolemia may contribute to the lack of GH suppression in diencephalic syndrome as well. However, 24-hour urine collections for cortisol were not obtained to confirm this finding. Cytokines play a prominent role in both stimulation and inhibition of GH, suggesting another mechanism for GH resistance during times of illness and stress.[24]

Another potential factor is ghrelin, a gastric hormone found to be a secretagogue for GH and to influence appetite and adiposity. In normal individuals, ghrelin is elevated in the fasting state and is suppressed acutely by food intake. Elevated fasting ghrelin levels in patients with starvation secondary to anorexia nervosa decrease with subsequent weight gain.[25] Ghrelin levels have not been studied in patients with diencephalic syndrome, but infusion of ghrelin into normal individuals has been shown to elevate GH without effecting

IGF-1 levels.[26] It is likely that ghrelin contributes to the control of energy homeostasis,[27] and dysregulation of ghrelin secretion may lead to loss of adipose tissue in the setting of elevated GH levels in diencephalic syndrome.

Leptin, an adipocyte hormone, has an essential role in regulation of metabolism and adiposity.[28] Leptin has been shown to rise with increases in adipose tissue, limiting further adipose accumulation. Leptin deficiency has been shown to result in severe, early obesity in children.[29] Therefore, dysregulation of leptin or the central hormones that regulate the production of leptin could also contribute to the severe loss of subcutaneous fat tissue in diencephalic syndrome. In addition, there are likely to be uncharacterized factors that contribute to the regulation of adipose mass and GH function.

CONCLUSIONS

Diencephalic syndrome is a rare but potentially lethal cause of failure to thrive in infants and young children that should be familiar to every practitioner who cares for young children. The diencephalic syndrome includes clinical characteristics of severe emaciation, normal linear growth, and normal or precocious intellectual development and a social disposition, which have been verified by case reports spanning the past half-century. Lack of hyperemesis, hyperalertness, or nystagmus should not be used to rule out this diagnosis. As the associated low-grade neoplasm can be aggressive, spinal imaging with gadolinium-enhanced MRI and cerebrospinal fluid analysis should be performed to determine the extent of the disease in patients with hypothalamic tumors, especially those with signs or symptoms of diencephalic syndrome. In addition, this unique model of partial GH resistance in the setting of normal linear growth provides evidence of the differential effects of GH stimulation on the metabolism of adipose tissue and linear growth. Multiple hypothalamic-pituitary factors involved in appetite regulation and metabolism are currently the object of scientific inquiry. Additional study of the perturbations of these factors in diencephalic syndrome should provide insight into the catabolic state, as well as provide clues to help in unraveling the feedback mechanisms that maintain the normal balance of caloric intake, weight regulation, and growth in young children.

ACKNOWLEDGMENTS

This work was supported in part by the Stop & Shop Family Pediatric Brain Tumor Clinic of the Dana-Farber Cancer Institute.

We gratefully acknowledge the contributions of Kimberly Nichols, MD, and Nyan Chu for assistance with laboratory assay descriptions.

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Pediatrics 2005;115;e742
DOI: 10.1542/peds.2004-2237