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.

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, Russell1 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, Aiddy and Hudson2 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.2-5 Nystagmus and vomiting were also noted in the majority of reported cases.2-5 In 1976, a review of 72 cases by Burr6 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 Francisco, Calif.) thereafter. IGF-I was measured by radioimmunoassay (RIA) or immunoradiometric assay (IRMA; Nichols Institute, San Francisco, Calif.) from 1987 onward. Adiposity was assessed by measurement of body mass index (BMI) in kilograms per square meter (kg/m²) or by body fat percentage (BFP) estimated by the bioelectrical impedance analysis (BIA) method. The diagnosis of diencephalic syndrome was based on the presence of severe emaciation, normal linear growth, and hypothalamic involvement on brain imaging studies. Growth hormone was measured at the time of presentation, at the time of tumor resection, and at follow-up (Table 1).
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-I) 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. 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%. 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, 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>
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<th>TABLE 1. Auxologic Data at Time of Diagnosis</th>
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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-
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
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, 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, hyperkinesia, and euphoria. In this series of 11 patients, vomiting was present in most of the cases. In addition, nystagmus with normal optic fundi, a flat fontanel, and the absence of clinical deficits. Four of the 11 patients eventually developed visual impairments, 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%. 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 paradoxical response to a glucose load. In the past 3 decades, several papers have attempted to explain the abnormal GH secretion evident in these conditions. However, by guest on August 20, 2021www.aappublications.org/news Downloaded from
patients. Pimstone et al\textsuperscript{16} reported on 2 children with
diencephalic syndrome and concluded that the cause of
the loss of subcutaneous fat was unlikely to be com-
pletely 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, Pim-
stone et al suggested that a yet unspecified dysregula-
tion of GH with subsequent mobilization of free fatty
acids might explain the clinical findings. Drop et al\textsuperscript{17}
hypothesized that a lipolytic peptide, $\beta$-lipotropin, pro-
duced 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 emaci-
tion to that seen in diencephalic syndrome but sec-
todary to extreme food restriction. Elevations in basal
and pulsatile GH values, with suppressed levels of
IGF-1, are found in this population.\textsuperscript{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 recom-
binant IGF-1 can suppress the GH release to some
degree but does not normalize growth hormone releas-
ing hormone–induced GH release.\textsuperscript{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 mainte-
nance of linear growth also differentiates this diagnosis
from that of other chronic illnesses or oncologic pro-
cesses. 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 dis-
tribution 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 an-
orexia nervosa include somatostatin dysregulation\textsuperscript{22}
and hypercortisolemia.\textsuperscript{23} The elevated random corti-
sol 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 resis-
tance during times of illness and stress.\textsuperscript{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 pa-
ients with starvation secondary to anorexia nervosa
decrease with subsequent weight gain.\textsuperscript{25} Ghrelin levels
have not been studied in patients with diencephalic
syndrome, but infusion of ghrelin into normal individ-
uals has been shown to elevate GH without effecting

\begin{table}
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\begin{tabular}{|c|c|c|c|c|c|}
\hline
Patient & Pathology & Surgery (subtotal Resection or Biopsy) & Second Resection & Chemotherapy & Radiation, cGy \\
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1 & Not done & Not done & Not done & Yes & 5000 \\
2 & Not done & Not done & Not done & Yes & 4000 \\
3 & Not done & Not done & Not done & Yes & 5000 \\
4 & Not done & Not done & Not done & Yes & 5000 \\
5 & Not done & Not done & Not done & Yes & 5000 \\
6 & Not done & Pilocytic astrocytoma & Pilocytic astrocytoma & Yes & 5000 \\
7 & Not done & Acute lymphoblastic leukemia & Pilocytic astrocytoma & Yes & 5000 \\
8 & Not done & Acute lymphoblastic leukemia & Pilocytic astrocytoma & Yes & 5000 \\
9 & Not done & Acute lymphoblastic leukemia & Pilocytic astrocytoma & Yes & 5000 \\
10 & Not done & Acute lymphoblastic leukemia & Pilocytic astrocytoma & Yes & 5000 \\
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\caption{Table 3. Treatment Course, Pathologic Diagnosis, and Outcomes}
\end{table}
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.

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.

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