CASE REPORT EAJNS 1(2): 34-40

Diencephalic Syndrome in a Pediatric Patient with a Suprasellar Lesion: Case Report and Review of Literature

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Summary

Diencephalic syndrome (DES) is an exceedingly rare condition with about 100 cases reported in literature. It presents as failure to thrive (FTT) in pediatric patients associated with central nervous neoplastic lesions in the suprasellar region. Its characteristic signs and symptoms are related to hypothalamic dysfunction, viz, emaciated body, normal linear growth, normal or precocious intellect, hyperalertness, hyperkinesia and euphoria. Such non-specific presentation usually delays diagnosis of the brain lesion. Herein, we present the case of a 3-year-old girl with diencephalic syndrome who presented to our neurosurgical unit. She had been earlier managed for malnutrition and presumed Pulmonary Tuberculosis without much improvement. Further management by the pediatric endocrinologist without change in condition prompted brain imaging. Brain MRI showed a large, avidly enhancing hyper-intense suprasellar lesion. Right pterional craniotomy with subtotal resection was done. Histopathology confirmed Hypothalamic Pilocytic Astrocytoma (WHO Grade 1) and the patient was referred to pediatric oncology for further management.

Keywords: *Diencephalic syndrome, failure to thrive, suprasellar tumor*

Introduction

Failure to thrive (FTT) is a relatively frequent problem in infancy and childhood commonly encountered by primary care physicians (1,2). The causes are legion, ranging from medical conditions to environmental factors such as child abuse or neglect (2). It is often defined as a weight-for-age value that falls below the fifth percentile on multiple occasions or weight deceleration that crosses 2 major percentile lines on a growth chart (3). Distinguishing the cause of FTT in these patients may prove challenging and all diagnostic efforts adopted should aim at this. The suspicion of an uncommon disease must come to the fore if dietary, medical and behavioral interventions have proved futile (1).

Diencephalic syndrome (DES) is a rare condition presenting with FTT in infants and children. It is associated with central nervous neoplastic lesions in the suprasellar region involving the hypothalamic-optic chiasmatic area (4). A few cases of posterior fossa lesions presenting similarly have also been reported (5). Patients present with profound emaciation despite adequate caloric intake, maintained linear growth, normal or precocious intellect, hyperalertness, hyperkinesia and euphoria. Other symptoms such as nystagmus, hydrocephalus and vomiting have additionally been associated with DES (1,2,6). It is a potentially lethal condition therefore rapid diagnosis and appropriate treatment are crucial for patient survival. Clinical signs and symptoms regress when the tumor is surgically extirpated or reduced by non-surgical therapy (1). Unfortunately, due to the non-specific nature of presentation and rarity, delayed diagnosis of DES is the norm rather than the exception (7).

Herein, we present the case of a 3-year-old girl with DES and FTT who presented to our neurosurgical unit. The diagnostic and therapeutic challenges faced are further discussed highlighting the importance of a high index of suspicion in such patients.

Case report

A 3-year-old girl referred from a rural facility presented with poor weight gain starting at 3 months of age (Figure 1). She was born full term with an unremarkable prenatal course. Perinatally, she was noted to have congenital talipes equinovarus (CTEV) of the right foot which was promptly corrected. No instigating event was identified as a possible trigger for the onset of poor weight gain. She had been exclusively breastfed and weaned at 6 months on a diet adequate in quality and quantity.

At 8 months of age, she was commenced on treatment for pulmonary TB based on a suggestive history (poor weight gain, night sweats, chronic cough) and a suspicious chest radiograph. This did not aid in weight gain although she continued to gain length/height normally (Figure 2). She had been on prolonged follow-up at the nutrition and pediatric clinics. At the time of presentation, she had a normal appetite and was eating regular table foods with adequate supplementation. She had suffered constipation since 8 months of age. In the preceding weeks, occasional early morning vomiting was noted. Developmental milestones were appropriate for her age with notable precocity in intelligence. She tired easily while playing with other children but was hyperalert with trouble sleeping and often kept the parents up at night. Her past medical history was otherwise unremarkable. On examination, she was noted to have severe emaciation; weight 8kg (Z score -3) with normal height 87cm (Z score -1), BMI Z score – 7.84). She had thin, brown, sparse hair and a normal head circumference (46cm) despite pseudohydrocephalic appearance due to severe loss of adipose tissue in the face (Figure 3). Dilated scalp veins were noted. She was hyperalert, playful, euphoric but easily irritable. Speech was normal. There was hypotonia of the lower limbs bilaterally with reduced power (MRC 4/5). She had tremors of the hands at rest. Visual acuity was normal. Fundoscopy revealed mild optic disc pallor despite a normal cup-disc ratio. The rest of the physical examination was unremarkable.

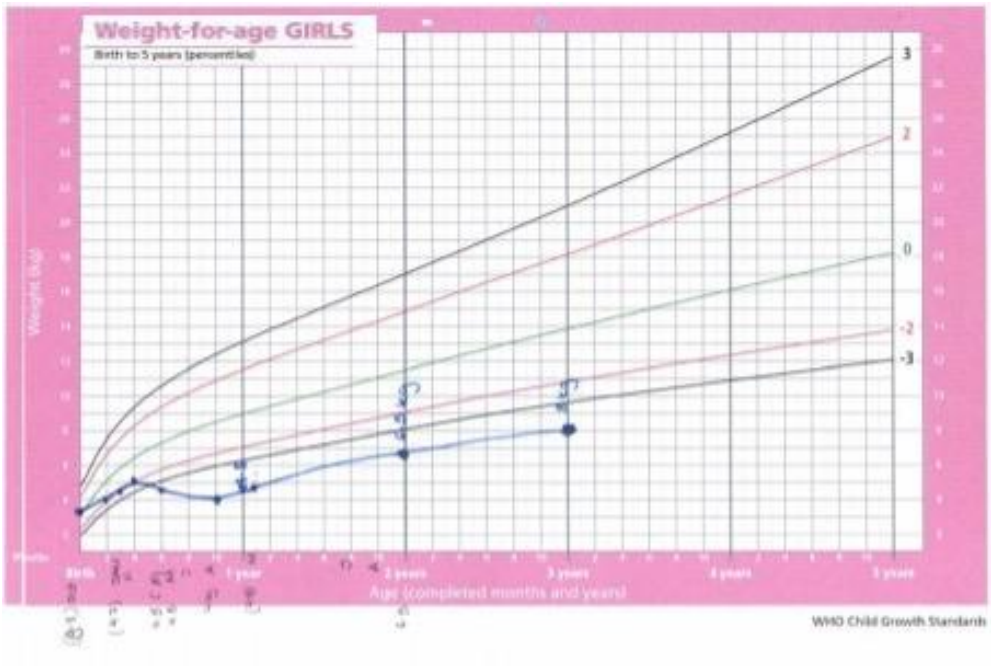

Figure 1: Weight-for-age chart of the patient showing weight gain trend from 3 months to 3 years. Note the consistently low Z-score (-3) from 1 year of age.

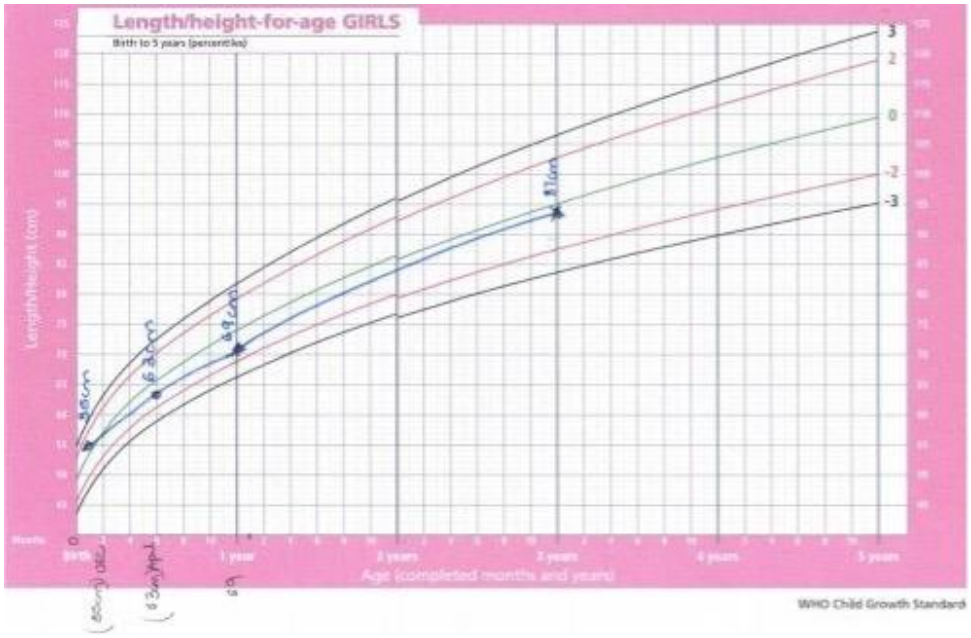

Figure 2: Length/height-for-age chart during the same period showing relatively normal height gain as opposed to the weight gain trends in figure 1.

Investigations

Initial work-up included the following: Full blood count- normal; Urea/Electrolytes/Creatinine- normal; Liver function tests- normal; Total protein levels- normal; Albumin levels- normal; Fasting blood sugar-normal; Ammonia levels- Elevated- 266.8µmol/L (11.0 – 51.0) repeat 318.6µmol/L; Urinalysis and urine electrolytes- normal; Urine reducing substances- not detected; Screening Echocardiogram- normal. Diabetes mellitus, hypercalcaemia, and diabetes insipidus were excluded as endocrine causes of FTT with normal laboratory test results (serum calcium, glucose and sodium) and lack of associated symptoms. Additional work-up to exclude hyperthyroidism, growth hormone deficiency, adrenal insufficiency and other pituitary hormonal abnormalities was also done revealing normal parameters.

A brain MRI was obtained showing a large, avidly enhancing suprasellar lesion filling the third ventricle with attendant reduction in cortical mantle thickness and ex vacuo hydrocephalus (Figure 4). The radiological diagnosis was hypothalamic glioma with a differential of craniopharyngioma.

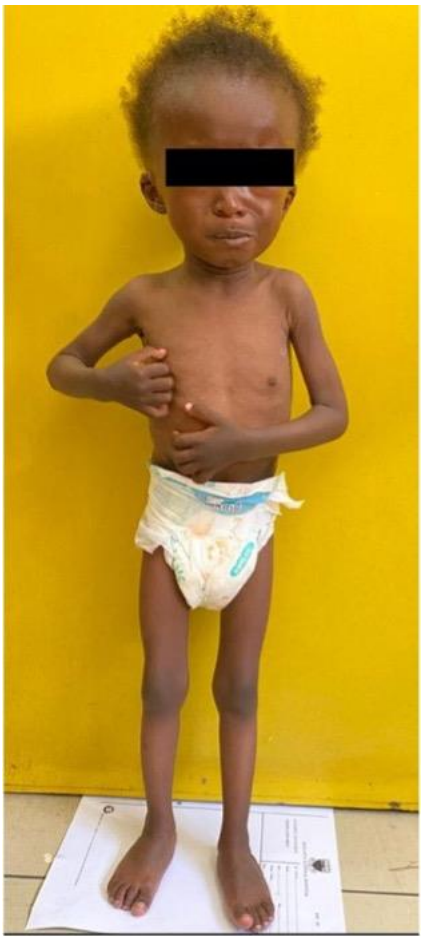

Figure 3: Picture of the patient at the time of presentation. Note the severe emaciation and thin, sparse hair. Normal head circumference despite severe loss of adipose tissue in the face gives the characteristic pseudo-hydrocephalic appearance.

Right pterional craniotomy with wide sylvian fissure dissection was subsequently performed. The lesion appeared pinkish white with cystic areas containing clear fluid. It was highly vascular and adherent to optico-carotid structures. Brisk bleeding encountered from tumoral vessels halted complete resection. Post-operatively, the patient had transient visual loss from which she recovered over subsequent weeks. She had an otherwise uneventful recovery.

Histopathological analysis confirmed the diagnosis of a Pilocytic Astrocytoma WHO Grade 1 (Figure 5). She was promptly referred to the pediatric oncology unit and commenced on an induction chemotherapeutic regimen consisting of Vincristine and Carboplatin. At the time of this report, she has received 8 out of 10 cycles. Baseline hematologic and renal parameters remain normal. She exhibits steady weight gain (currently 13kgs from an initial 8kgs) and is due for a follow-up MRI upon completion of her 10th cycle of chemotherapy to monitor effectiveness of treatment.

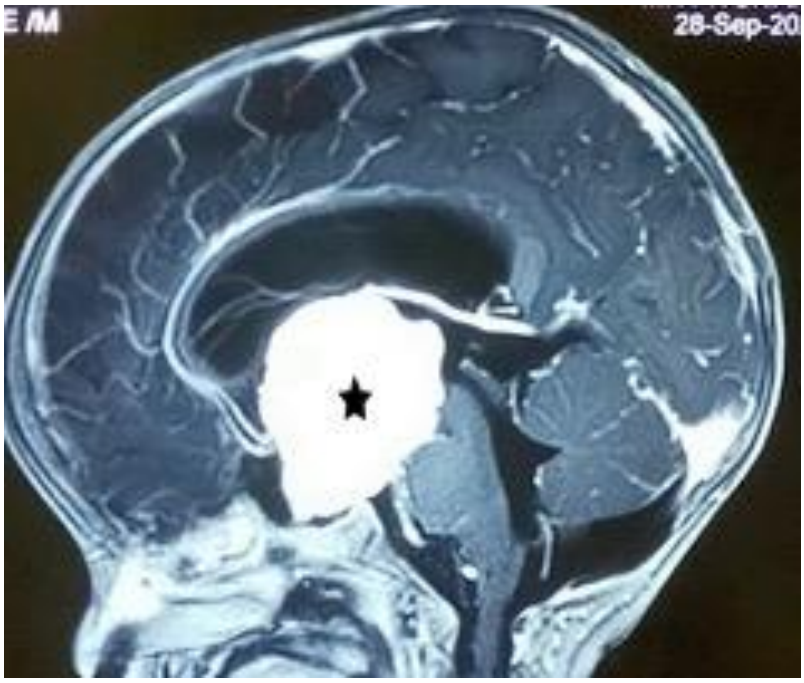

Figure 4: T1-weighted sagittal image after gadolinium enhancement demonstrating a large sellar/suprasellar lesion (starred) with avid contrast uptake, involving the hypothalamic region, extending into the 3rd ventricle and distorting the brainstem posteriorly

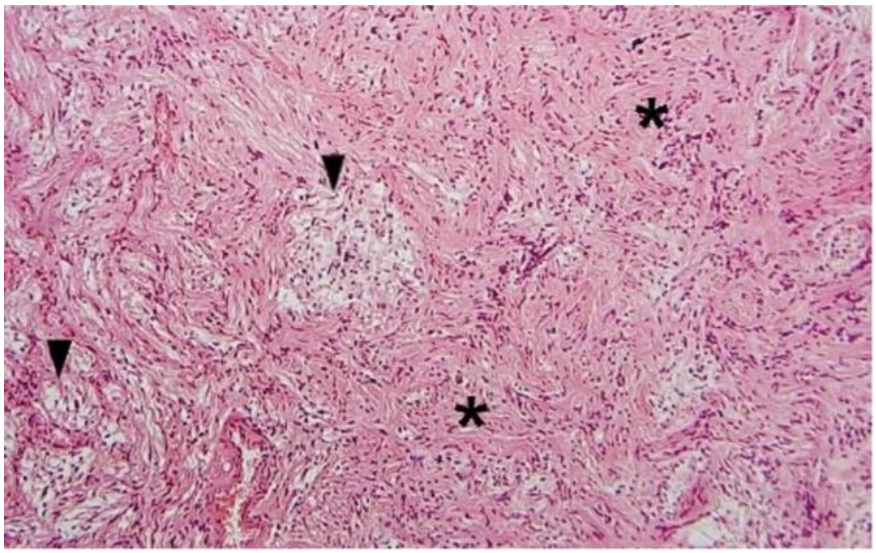

Figure 5: Pictomicrograph of histopathological section (H/E stain) at low power showing a characteristic biphasic appearance with compact, cellular areas embedded in a fibrillary matrix (*) and loose, less cellular areas with scattered astrocytic cells and microcysts (arrowhead). Pilocytic Astrocytoma (WHO Grade 1) was the final diagnosis

Discussion

DES, also known as Russell syndrome or diencephalic cachexia was first described by Russell in 1951. In his landmark paper, he detailed a series of 12 patients who presented with profound emaciation during infancy associated with the loss of subcutaneous fat despite normal or slightly reduced calorie intake, preservation of linear growth, nystagmus, and hyperkinesis. Subsequent imaging in all the patients would in turn reveal intracranial lesions involving the anterior hypothalamus or optico-chiasmatic gliomas (4). In 1972, Addy and Hudson reported a series of 3 patients and further reviewed literature summarizing a total of 48 similar cases (5) Since then, work on DES has largely comprised of multiple case series and case reports with the most recent review by Klochkova *et al.* in 2017 finding approximately 100 cases of DES in literature (8).

The clinical manifestations of DES can be categorized into major features **(**severe emaciation despite adequate caloric intake i.e., FTT, locomotor hyperactivity, euphoria) and minor features (skin pallor without anemia, hypoglycemia, hypotension). It may also be associated with locomotor hyperkinesis (e.g., tremors, dystonia, tics) normal height and endocrine dysfunction (8,9). Patients also present with neurological sequelae such as nystagmus, decreased visual fields, and optic pallor seen in 56%–66% of the cases (2). Obstructive hydrocephalus, owing to the position of the lesions in the sellar/suprasellar region, with attendant vomiting and headaches may be the initial indication of an intracranial mass lesion in DES patients (1, 2, 6, 9). Mean age of symptom onset is 18±10.5 months with diagnosis delayed by about 11±9.7 months (2, 7). In our case, despite the presence of salient clinical features indicative of DES, diagnosis was delayed by about two and a half years. A similar duration of delay was also reported by Guru and Harshad in India. In addition to the non-specific nature of presentation and low index of suspicion amongst clinicians, high prevalence of illiteracy, poverty and limited availability of healthcare facilities/specialists contribute greatly to such delays in developing countries (9).

Tumors related with DES are usually optic pathway/hypothalamic gliomas with histopathology mostly showing a pilocytic (WHO-grade I) or, to a lesser extent, pilomyxoid (WHO-grade II) astrocytoma picture (1). Rarely, Anaplastic astrocytomas, craniopharyngiomas and posterior fossa tumors have been implicated (2, 5, 9). Not all patients with such sellar/suprasellar lesions develop DES and the exact pathophysiology isstill not well understood (2, 9). It is unclear whether weight loss in DES patients isdue to increased energy consumption, inadequate absorption, or both (1). Various hypotheses have been postulated. The most pervasive is that release of hypothalamic growth hormone–releasing factors by the intracranial neoplasm produces paradoxical response to hyperglycemic or hypoglycemic events (10). Involvement of the hypothalamus probably results in elevation of growth hormone and ghrelin with resultant decreased insulin and leptin levels. Conversely, however, these hormonal changes wereclaimed by other workers to be related to patients' nutritional status, rather than causality (10, 11, 12). Dysregulated release ofβ-lipotropin (a lypolytic peptide) produced in excess by either primary neoplasm or as a secondary effect to invasion of the hypothalamus may cause excessive lipolysis and almost complete loss of subcutaneous tissue producing the characteristiccachectic appearance (13). Further adding to this conundrum, routine endocrine hormonal assessment may be completely normal (11) as was the case in our patient.

Existing literature shows that most patients with an eventual diagnosis of DES have extensive clinical work-up before arrival at diagnosis (14). This is largely due to the fact that a brain tumor is not considered early (2). DES should therefore be included as a differential in any child with FTT and normal linear growth regardless of the absence of neurological symptoms. Diagnostic imaging

is key in confirming presence of the primary intracranial pathology. The more widespread availability of CT scan plays an important screening role, while a brain MRI study further describes location, epicenter, extension, associated hydrocephalus, ventricular involvement, and encasement of vital neurovascular structures (9).

In the management of patients with DES and FTT, a reductive approach of supplemental feeding without any further intervention is not sufficient to reverse the syndrome, as emaciation and tumor growth remain progressive (1). Mean survival of non-treated DES is usually less than a year (15). As such, surgery (complete/partial resection), chemotherapy and/or radiation therapy are modalities aptly applied (2). This takes cognizance of the inherent biological nature, location and growth pattern of the attendant intracranial neoplasm. Despite total extirpation being potentially curative for WHO-grade 1 lesions, maximum safe resection should be the aim (9). Gross total resection remains elusive as intimate involvement of the tumor with visual pathways, anterior circulation and hypothalamo-pituitary structures precludes radical surgical strategies (1, 2, 9). Further, the Baby Pediatric Oncology Group I study indicated that the degree of resection had minimal influence on overall survival of patients with low grade optic-hypothalamic gliomas (16). Radiotherapy, though effective in control of primary disease, is oft accompanied by undesirable neurocognitive and endocrinologic sequelae. It is thus avoided in pediatric patients (17).

Encouraging results have been observed with chemotherapy of optico-chiasmatic and hypothalamic gliomas following accurate histological diagnosis (9). Low dose regimens of cisplatin and etoposide are successful in controlling low grade disease with reduced neurotoxicity and myelotoxicity (18). The outcome for patients with high-grade astrocytomas remains poor despite aggressive surgical resection, radiotherapy and high-dose adjuvant chemotherapy (1). A promising approach in such patients has been the inclusion of autologous hematopoietic stem cell rescue following high-dose chemotherapy. This counter-acts the marrow-ablative nature of chemotherapeutic agents with improvement in survival (1, 19).

Proper control of primary disease following surgery with/without adjuvant treatment results in resolution of DES and weight gain progressing to normal levels within 2 years (9). Adequate nutritional support aids in recovery and should be established as soon as possible. Oral feeds are the first choice. In patients unable to attain adequate intake orally, additional enteral feeding via gastrostomy is widely used as it is relatively safe. Parenteral nutrition should only be considered if enteral methods fail (2).

In conclusion, DES remains a fairly infrequent but altogether important cause of FTT in infants and young children. Pediatricians, endocrinologists and neurosurgeons should be aware of its existence and inextricable association with intracranial neoplasms in the hypothalamic region. This avoids prolonged application of futile approaches otherwise effective for commoner causes of FTT. A high index of suspicion and neuroimaging enable early confirmation of diagnosis. Prompt surgical and chemotherapeutic intervention with judicious nutritional support portend a favorable prognosis. A multi-disciplinary approach ensures holistic management with good outcomes.

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