Child Neurology:

Diencephalic syndrome–like presentation of a cervicomedullary brainstem tumor

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ABSTRACT

Diencephalic syndrome is a rare clinical entity, traditionally encompassing severe failure to thrive, nystagmus, and hyperkinesia, secondary to an intracranial neoplasm that is classically located in the hypothalamic region and its vicinity. However, the presenting features can be variable, often resulting in delayed diagnosis, which may worsen prognosis. This case report describes the atypical presentation of a posterior fossa tumor with features reminiscent of diencephalic syndrome that have not previously been reported in the literature. We report a 21-month-old girl with a cervicomedullary brainstem astrocytoma, who presented with isolated gross motor developmental delay, decreased growth velocity, and stridor. The neurologic signs frequently reported in patients with diencephalic syndrome were absent; however, severe failure to thrive was present. This case broadens the etiologic differential diagnosis of diencephalic syndrome in addition to the traditional hypothalamic region tumor location. This case urges physicians to consider central neurologic processes in the differential diagnosis of children with refractory failure to thrive with or without classical features of diencephalic syndrome, in whom etiology is not identified by routine investigations, given its importance in determining prognosis and management.

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GLOSSARY

DS = diencephalic syndrome; **FTT** = failure to thrive; **GH** = growth hormone; **IGF-1** = insulin-like growth factor-1; **NG** = nasogastric.

While failure to thrive (FTT) is a common clinical entity, diencephalic syndrome (DS) is a rare but life-threatening cause. Russell¹ first described DS in 1951, based on a series of 5 children with hypothalamic neoplasms. Associated signs included profound emaciation, maintained linear growth, locomotor hyperactivity, euphoria, skin pallor, hypotension, and hypoglycemia.¹ Other case series have reported nystagmus, visual field defects, headache, and emesis.²

We report a DS-like presentation of a posterior fossa tumor in a 21-month-old girl, in whom linear growth was not maintained, isolated gross motor delay was present, and significant respiratory symptoms, including chronic cough and stridor, developed.

CASE PRESENTATION The patient was born at 36 weeks gestation with no complications. Birthweight was 2.04 kilograms (3rd percentile), length was 46 centimeters (15th–50th percentile), and head circumference was not documented. She was breast and formula fed until 6 months of age, then transitioned to solids, at which point her weight was 5.4 kilograms (<3rd percentile). During this time, she developed recurrent vomiting with minimal response to antireflux medications. She also developed a chronic cough. Her weight gain plateaued after 6 months of age. She was referred to the FTT clinic at 11 months with a weight of 5.95 kilograms (<3rd percentile), height of 68 centimeters (3rd–15th percentile), and head circumference of 44 centimeters (15th–50th percentile). Around 17 months, she developed inspiratory stridor while sleeping. Increasing caloric intake was unsuccessful, and nasogastric (NG) feeds were initiated at 18 months. Despite NG insertion, she continued to experience daily vomiting. Sweat chloride, celiac screen, thyroid function testing, immunoglobulins, endoscopy, gastric emptying study, and laryngoscopy failed to reveal any diagnoses.

Supplemental data
at Neurology.org

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At 21 months, the patient was hospitalized for further investigation. Her weight was 6.5 kilograms and length was 71 centimeters, both significantly below the 3rd percentile. She had been below the 3d percentile for weight and height since 5 and 12 months, respectively. Her head circumference was 46.5 centimeters (25th–50th percentile), demonstrating stable growth from previous values (figure e-1 at Neurology.org). Parental heights were 160 centimeters (25th–50th percentile) and 175 centimeters (25th–50th percentile) for her mother and father, respectively.

Developmental review revealed isolated gross motor delay. The patient crawled at 10 months, cruised around 12 months, and was unable to walk independently at 21 months. On examination, she was alert and appropriate, but not euphoric. She was emaciated, nondysmorphic with thin hair, and had intact cranial nerves with no nystagmus. Fundoscopic examination results were normal. There was mild peripheral hypotonia noted symmetrically, reflexes were 3+ throughout, and plantar reflexes were down-going. There was no dysmetria.

The neurology team was consulted to determine the etiology of the patient's developmental delay. An MRI brain was performed, which showed an exophytic lesion arising from the dorsal medulla measuring $3.7 \times 4 \times 3.8$ cm with secondary obstructive hydrocephalus (figure 1). Urgent neurosurgical consultation led to

partial tumor resection. Pathology was consistent with cervicomedullary pilocytic astrocytoma, and immunohistochemical analyses were negative for BRAF V600E and p53 mutations. Fluorescence in situ hybridization for 7q34 tandem duplication, to detect *BRAF-KIAA1549* fusion, was also normal. Subsequently, the patient was started on vinblastine chemotherapy.

Prior to surgical resection, the patient had a random growth hormone (GH) level of 1.4 $\mu\text{g/L}$ (normal) and insulin-like growth factor-1 (IGF-1) of 62.0 $\mu\text{g/L}$ (normal). Since surgery was urgent, GH stimulation studies were not obtained. As the patient had just completed a 70-week chemotherapy regimen, postresection GH studies have not been conducted.

Postresection, the patient continued to require NG feeds with no emesis, and ultimately a gastrostomy tube was inserted to meet nutritional needs. She achieved significant gains in her gross motor development, but continued to exhibit delays. She was walking with assistance shortly after her second birthday, and walking independently by 2.5 years. An MRI completed 16 months postresection shows a tumor size of $2.4 \times 2.8 \times 2.4$ centimeters. At her most recent follow-up, 17 months postresection, her height was 89.2 centimeters (3rd–10th percentile) and her weight was 14.6 kilograms (50th percentile). Her stridor has improved significantly, due to a resolving right vocal cord palsy and decreasing tumor size.

Figure 1 Pilocytic astrocytoma

T2-weighted fluid-attenuated inversion recovery (FLAIR) axial (A), T1-weighted sagittal (B), coronal (C), and postcontrast sagittal (D) images demonstrate an exophytic tumor arising from the dorsal medulla, representing a pilocytic astrocytoma. The tumor is T1 hypointense, T2 FLAIR hyperintense with heterogeneous enhancement, causing obstructive hydrocephalus with periventricular edema.

DISCUSSION The exact incidence of DS is unknown. In our tertiary care center, only 9 cases have been recorded in the last 15 years.³ According to a review of 72 patients, the mean age at symptom onset is 6.2 months.⁴ However, the diagnosis is frequently delayed, with an average age at diagnosis of 23 months (range 4–56 months).⁵

Various clinical findings have been associated with DS, but the constellation of FTT, nystagmus, and hyperkinesia with euphoria is considered most suggestive.⁶ However, a recent study reported that only 5/9 patients had nystagmus and 3/9 had hyperkinesia.³ Apart from FTT and recurrent emesis, our patient had none of the previously reported neuropsychiatric symptoms, making diagnosis of DS particularly challenging.

Classically, DS is caused by tumors located in the diencephalon, including optic and hypothalamic astrocytomas. However, approximately 9% of tumors are located elsewhere, including the posterior fossa and anterior hypothalamus.⁴ Posterior fossa tumors have been frequently grouped under DS due to significant overlap in clinical features.⁴ In one series, 6 of 67 cases had tumors in the posterior fossa. All 6 cases presented with vomiting, compared to 35/61 cases in the anterior fossa group. Nystagmus, optic atrophy, and tremor were more frequently seen in the anterior

fossa group while FTT, hyperactivity, and pallor were equal in both groups.⁴ One hypothesis for the clinical overlap is that posterior fossa tumors may interfere with the locus ceruleus and fourth ventricle, from where the hypothalamus receives significant neuronal input.⁴ The FTT seen with posterior fossa tumors is unexplained by vomiting or decreased intake, but has been associated with lower cranial nerve palsies and resultant dysphagia or absent gag reflex.⁷

Unique to our case is the delay in linear growth velocity as opposed to the classical DS cases. In one series, all 11 patients had heights between the 10th and 97th percentile, whereas our case demonstrated profound decrease in height velocity from 11 months onwards.⁵ Linear growth is less well-studied in the posterior fossa tumor subgroup. Of 7 described posterior fossa tumor cases with FTT in the literature, only one report of a 4½-year-old girl, with a disseminated pilocytic astrocytoma involving both the diencephalon and brainstem, noted height less than the 3rd percentile.⁸ Conversely, a study looking at growth parameters in 22 children with brainstem tumors found that 5 had heights less than the 1st percentile.⁷ Perhaps, then, it is the tumor location rather than DS itself that determines whether linear growth velocity is maintained.

There is increasing focus on the role of GH in the pathogenesis of DS. In one case series, 6/7 patients had elevated basal GH, and none had appropriate suppression of GH following a glucose load.⁵ Increased GH levels may be secondary to release of GH-releasing factors from the hypothalamus.² The lipolytic activity of the excess GH might account for the absence of subcutaneous fat seen in children with DS.⁹ All 7/7 patients had normal IGF-1 levels, suggesting a relative GH-resistant state.⁵ There are insufficient data to explore whether GH secretion differs based on tumor site. However, our patient had GH and IGF-1 levels within normal range, likely because of the tumor's location in the posterior fossa.

Our patient's gross motor delay was also of interest. This has not been reported in other case series, but is likely attributable to the tumor's location. More peculiar was the lack of cerebellar signs given the vermal and cerebellar hemisphere localization. This may be explained by slow growth and chronicity of the tumor. Another unusual finding was the respiratory symptoms, including stridor and cough. Arising from the dorsal medulla, the tumor likely affected the central respiratory drive with involvement of the vagus or recurrent laryngeal nerve.

The exact prognosis of DS is unknown. However, in one case series of 11 patients, the mortality rate was 55%.⁵ The presence of spinal seeding is associated with poor prognosis, emphasizing the importance of early diagnosis.^{5,10}

Astrocytomas associated with DS tend to be larger, more aggressive, and occur at a younger age than those without DS.² Astrocytomas or gliomas have been found to harbor a *BRAF-KTAA1549* fusion gene, *NF1* mutations, or loss of function of the *p53* gene.^{3,11} In our center, 5 of the 9 cases had the *BRAF* fusion gene and 2 had known neurofibromatosis type 1.³ Whether prognosis differs based on underlying genetic etiology is not known.

This case broadens the DS-like phenotype previously reported; the patient's linear growth and gross motor development were both affected, while her neurologic examination was normal. In addition, she had respiratory symptoms, including stridor and cough, explained by the tumor's vicinity to the dorsal medulla. While the term DS has been used previously to encompass posterior fossa tumors presenting with FTT, the observed differences in phenotype based on anatomic location may eventually warrant new terminology. Therefore, this case demonstrates the importance of maintaining a high index of suspicion for DS presentation of hypothalamic and posterior fossa tumors when evaluating young children with unexplained FTT.

AUTHOR CONTRIBUTIONS

Dr. Conway gathering the initial case information, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Ejaz gathered the initial case information, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Kouzmitcheva reviewed and revised the manuscript and approved the final manuscript as submitted. Dr. Savlov analyzed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr. Rutka analyzed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr. Moharir analyzed and interpreted the data, supervised the gathering of case information, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. All authors approved the manuscript as submitted and agree to be accountable for all aspects of the work.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Russell A. A diencephalic syndrome of emaciation in infancy and childhood. *Arch Dis Child* 1951;26:274.
2. Poussaint TY, Barnes PD, Nichols K, et al. Diencephalic syndrome: clinical features and imaging findings. *AJNR Am J Neuroradiol* 1997;18:1499–1505.
3. Kilday JP, Bartels U, Huang A, et al. Favorable survival and metabolic outcome for children with diencephalic syndrome using a radiation-sparing approach. *J Neurooncol* 2014;116:195–204.
4. Burr IM, Slonim AE, Danish RK, Gadoth N, Butler IJ. Diencephalic syndrome revisited. *J Pediatr* 1976;88:439–444.

5. Fleischman A, Brue C, Poussaint T, et al. Diencephalic syndrome: a cause of failure to thrive and a model of partial growth hormone resistance. *Pediatrics* 2005;115:742–748.
6. Diamond EF, Averick N. Marasmus and the diencephalic syndrome. *Arch Neurol* 1966;14:270–272.
7. Lehman RA, Krishnamurthy S, Berlin CM. Weight and height deficits in children with brain stem tumors. *Clin Pediatr* 2002;41:315–321.
8. Distelmaier F, Janssen G, Mayatepek E, Schaper J, Göbel U, Rosenbaum T. Disseminated pilocytic astrocytoma involving brain stem and diencephalon: a history of atypical eating disorder and diagnostic delay. *J Neurooncol* 2006;79:197–201.
9. Pimstone BL, Sobel J, Meyer E, Eale D. Secretion of growth hormone in the diencephalic syndrome of childhood. *J Pediatr* 1970;76:886–889.
10. Kim A, Moon JS, Yang HR, Chang JY, Ko JS, Seo JK. Diencephalic syndrome: a frequently neglected cause of failure to thrive in infants. *Korean J Pediatr* 2015;58:28–32.
11. Nozaki M, Tada M, Kobayashi H, et al. Roles of the functional loss of p53 and other genes in astrocytoma tumorigenesis and progression. *Neuro Oncol* 1999;1:124–137.

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