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CENTRAL NEUROGENIC HYPERVENTILATION AND RENAL TUBULAR ACIDOSIS IN CHILDREN WITH PONTINE GLIOMAS

Central neurogenic hyperventilation (CNH) is a rare neurologic condition that develops secondary to brainstem involvement. Approximately 35 noncomatose patients with CNH have been reported, including 7 with either a diffuse (patients 2–10 in the table) or focal (patient 1 in the table) brainstem glioma.^{1–7} Although diffuse intrinsic pontine glioma (DIPG) is the most common pediatric brainstem cancer, only one case report described a child with DIPG who experienced CNH.⁶

We report a series of children with DIPG and CNH treated at our institution. Our results suggest that the association between CNH and DIPG may not be as rare as previously believed. We also showed unique clinical consequences of CNH, particularly the occurrence of secondary distal renal tubular acidosis (RTA).

Methods. Once institutional review board approval was obtained, we reviewed the clinical and radiologic characteristics of all patients with DIPG and CNH treated at our institution from July 1, 2010, until June 30, 2013. CNH was defined as the occurrence of age-specific tachypnea of unknown origin while awake and during sleep accompanied by an elevated blood pH (above 7.45) and hypocapnia. Cardiovascular and pulmonary disorders, or use of medications associated with CNH, were ruled out in all patients.

Results. Three of 68 (4%) patients with DIPG seen at our institution during the study period met the diagnostic criteria for CNH (table). CNH was diagnosed concomitantly with clinical and radiologic tumor progression in all patients. Two patients had previously received anticancer therapy, including radiotherapy. Patient 9 had been initially misdiagnosed with encephalitis 2 months before the simultaneous diagnosis of DIPG and CNH. All patients had radiologically typical DIPGs by brain MRI. All 3 patients died of progressive disease after a median survival of 11 months (range 9–14 months). Brain-only autopsy confirmed the diagnosis of glioblastoma (World Health Organization grade 4) in 2 patients.

The median interval between first radiologic documentation of DIPG and CNH was 6 months (range 2–10 months). Patients 8 and 10 developed CNH

5 and 8 months after completion of radiotherapy, respectively. Whereas patients 8 and 9 had overt tachypnea at presentation with CNH, patient 10 had no symptoms despite an increased respiratory rate compared to baseline. All patients had decreased serum bicarbonate (range 12–15 mmol/L) and phosphate (range 2.1–2.6 mg/dL) at diagnosis of CNH. Patient 9 also had hypokalemia (serum potassium 3.0 mmol/L). Analysis of venous blood gas demonstrated a primary chronic respiratory alkalosis and compensatory metabolic acidosis in all patients. Analysis of urinary electrolytes in patients 9 and 10 showed an unbalanced anion gap (sum of the random urinary concentrations of sodium and potassium far exceeded the random urinary concentration of chloride) suggestive of a decreased net acid excretion by the kidneys and compatible with the diagnosis of distal RTA.

CNH improved with the initiation of corticosteroids in patient 8 and during the course of radiotherapy in patient 9. Patient 10 experienced rapid neurologic worsening and died of tumor progression within 1 week of onset of CNH.

Discussion. Although only one child with DIPG had been previously reported to develop CNH,⁶ our experience showed that this phenomenon may not be as rare as previously recognized, particularly at tumor progression. We acknowledge that the true incidence of CNH may be an underestimate because of our strict diagnostic criteria and since this phenomenon may remain undetected in children with milder presentations or those at terminal stages who receive palliative care at home. Furthermore, the diagnosis of CNH is dependent on the awareness of clinicians to investigate the etiology of tachypnea with or without electrolyte abnormalities. Although electrolyte abnormalities had been previously described concomitantly with CNH,⁴ we reported the secondary occurrence of RTA, a known consequence of chronic respiratory alkalosis due to other etiologies.

As previously described,^{1–6} we used opioids in one of our patients to treat the symptoms associated with CNH. We could not assess the response since this patient died within a few days. Although all 3 patients had a brain MRI with spectroscopy at diagnosis of CNH, and 2 of them a brain-only autopsy, they did not provide any new data to further elucidate the pathophysiology of this phenomenon.

Supplemental data
at Neurology.org

Table Characteristics of patients with brainstem gliomas and central neurogenic hyperventilation

	Age, y ^b /sex	Tumor location	Histologic diagnosis	Characteristics of CNH ^a			
				Respiratory rate/min	pH	CO ₂ , mm Hg	Reference
1	7/F	Pons and medulla	Pilocytic astrocytoma (focal tumor)	52	7.58	7.7 (Ar)	3
2	11/M	Pons and medulla ^c	NA ^d	72	7.51	9 (V)	6
3	25/F	Pons and medulla ^c	NA ^d	30	7.61	11 (Ar)	1
4	29/M	Pons and medulla ^c	NA ^d	28	7.5	20 (Ar)	7
5	32/F	Pons and medulla	Anaplastic astrocytoma	36	7.66	7.6 (Ar)	2
6	53/F	Pons and medulla ^c	Astrocytoma ^e	22	7.74	9 (Ar)	4
7	57/M	Pons ^c	Low-grade astrocytoma ^e	30	7.72	6 (Ar)	5
8	4.8/F	Pons, medulla, and midbrain ^c	Glioblastoma ^e	28	7.47	17 (V)	Current report
9	10.5/M	Pons and middle cerebellar peduncle ^c	NA ^d	32	7.61	13 (V)	Current report
10	16.1/F	Pons, medulla, and midbrain ^c	Glioblastoma ^e	28	7.5	18 (V)	Current report

Abbreviations: Ar = arterial; CNH = central neurogenic hyperventilation; NA = not available; V = venous.

^a Worst nonsimultaneous clinical and laboratory parameters documented during the course of CNH.

^b Age at diagnosis of brainstem glioma.

^c Tumor location was evaluated concomitantly with the diagnosis of CNH by brain MRI in 7 patients (patients 2, 3, 4, 7, 8, 9, and 10) or at autopsy (patient 6). Tumor location in patients 1 and 5 was evaluated by MRI at the diagnosis of brainstem glioma and approximately 3 months before the diagnosis of CNH.

^d These patients had radiologic findings in brain MRI at diagnosis that precluded the need for histologic confirmation (figure e-1 on the *Neurology*[®] Web site at Neurology.org).

^e Histologic confirmation obtained at autopsy.

We hope that our experience will raise awareness about the occurrence of CNH in children with DIPG. The concomitant occurrence of low serum bicarbonate and electrolyte abnormalities suggestive of RTA in such patients may strengthen the suspicion of CNH.

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