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Clinical Observations

Rapid-Onset Obesity With Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation (ROHHAD) Syndrome May Have a Hypothalamus–Periaqueductal Gray Localization

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ABSTRACT

BACKGROUND: Anatomical localization of the rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) syndrome has proved elusive. Most patients had neuroimaging after cardiorespiratory collapse, revealing a range of ischemic lesions. **PATIENT DESCRIPTION:** A 15-year-old obese boy with an acute febrile encephalopathy had hypoventilation, autonomic dysfunction, visual hallucinations, hyperekplexia, and disordered body temperature, and saltwater regulation. These features describe the ROHHAD syndrome. Cerebrospinal fluid analysis showed pleocytosis, elevated neopterins, and oligoclonal bands, and serology for systemic and antineuronal antibodies was negative. He improved after receiving intravenous steroids, immunoglobulins, and long-term mycophenolate. Screening for neural crest tumors was negative. **CONCLUSION:** Magnetic resonance imaging of the brain early in his illness showed focal inflammation in the periaqueductal gray matter and hypothalamus. This unique localization explains almost all symptoms of this rare autoimmune encephalitis.

Keywords: ROHHAD syndrome, autoimmune encephalitis, periaqueductal gray matter, hypothalamus

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Introduction

The rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD) syndrome is increasingly recognized to have an underlying autoimmune pathobiology. We report a boy

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with encephalopathy, seizures, diabetes insipidus, hypoventilation, autonomic dysregulation, and visual hallucinations—a constellation of symptoms that describe the ROHHAD syndrome—with neuroimaging evidence of focal inflammation in the periaqueductal gray matter and hypothalamus.

Patient Description

A 15-year-old ethnic Chinese boy was admitted to the hospital with a 4-day history of fever, headache, and vomiting. There were no sick contacts or recent travel. His history was remarkable for weight gain since 9 years of age (his body mass index increased from the 50th to >97th centile). He was adopted at birth and his family history was unavailable.

Admission weight was 87 kg and height 1.74 m (body mass index 28.7 kg/m^2). He looked flushed and was febrile (maximal temperature 39.5°C). He remained alert and oriented to his surroundings, had mild neck stiffness, and brisk patellar reflexes with no other abnormal signs. Opening pressure on lumbar puncture was 30 cmH_20, and cerebrospinal fluid analysis showed normal white cell counts (4 cells/mm^3), but increased protein (1.42 g/L) and red cells (570 cells/mm^3) from a hemorrhagic tap. Polymerase chain reaction tests were negative for herpes simplex virus and enterovirus DNA. Blood and cerebrospinal fluid cultures were sterile and cranial computed tomography was normal. Intravenous antibiotics for encephalitis (ceftriaxone, ciprofloxacin) were administered. Nasopharyngeal aspirate polymerase chain reaction returned positive for respiratory syncytial virus and rhinovirus.

Over the week, he had increasing irritability, lethargy, and somnolence. On days 6 and 7 of illness, he was intermittently hypothermic (as low as 34°C), had periods of shallow breathing in sleep without desaturation, and had a brief focal clonic seizure of the left arm that was aborted with intravenous lorazepam 4 mg. As breathing became more labored, he was electively intubated and mechanically ventilated in the intensive care unit.

Significant polyuria from diabetes insipidus ensued (urine output 9.5 mL/kg/hour; highest serum sodium 150 mmol/L, paired serum and urine osmolarity 317 mOsm/kg and 235 mOsm/kg, respectively). This responded well to intranasal desmopressin 20 mcg twice daily. Features of autonomic instability became increasingly apparent: temperature dysregulation, labile blood pressure requiring inotropes, loss of the tachycardic response to hypotension, urinary retention, constipation, and feed intolerance necessitating a nasojejunal tube placement. The anal and cremasteric reflexes were preserved.

Magnetic resonance imaging (MRI) of the brain on day 7 of illness showed T2 hyperintensity in the periaqueductal gray matter (Fig 1A-C), splenium of the corpus callosum, and the right caudate nucleus. Restricted diffusion was evident only in the lesion at the corpus callosum. The pituitary stalk appeared bulky and showed gadolinium enhancement (Fig 2 A,B). MRI of the spinal cord was normal. Repeat cerebrospinal fluid studies performed 1 week after the initial lumbar puncture showed elevated white cells (26 cells/mm^3) and protein (0.83 g/L), but no blasts or malignant cells, and negative polymerase chain reactions or serology for herpes simplex virus, enterovirus, Epstein-Barr virus, Japanese encephalitis virus, *Mycobacterium tuberculosis*, *Cryptococcus* spp., and *Mycoplasma pneumoniae*. Oligoclonal bands were absent but neopterin levels were markedly elevated (274 nmol/L; normal 6-30) in the cerebrospinal fluid. An alpha coma pattern was seen on electroencephalography.

Presuming an autoimmune etiology, he was given intravenous methylprednisolone 1 g for 5 days (beginning on day 8 of illness), followed by maintenance doses at 80 mg daily. In the next 2 days, improvements were seen in blood pressure control and body temperature. Inotropes and desmopressin were successfully discontinued.

Though consciousness returned and seizures were controlled, he remained intubated because of persistent mucous plugging in the left main bronchus and significant hypoventilation in sleep. He was successfully weaned to noninvasive ventilation on day 8 of steroids (day 16 of illness). Exaggerated startles and myoclonus in response to touch and stimulation resembling hyperekplexia were noted at this point. He also experienced fearful visual hallucinations—the medical team were perceived to be wielding knives and meaning to stab him, and the noninvasive ventilation mask transformed into school textbooks that were weighing heavily on his face. Serum sodium dropped to 123 mmol/L despite normal urine volumes (1.2 mL/kg/hour), suggestive of a syndrome of inappropriate antidiuretic hormone secretion. In view of these new symptoms, he was given intravenous immunoglobulins 2 g/kg over 4 days. After day 2 of intravenous immunoglobulin treatment, he was able to breathe without assistance (day 18 of illness).

Serum anti-aquaporin 4 antibody was negative, as were systemic (antinuclear, double-stranded DNA and extractable nuclear antigens), and other antineuronal antibodies (N-methyl-D-aspartate receptors, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors-1 and 2, gamma-aminobutyric acid B receptors, voltage-gated

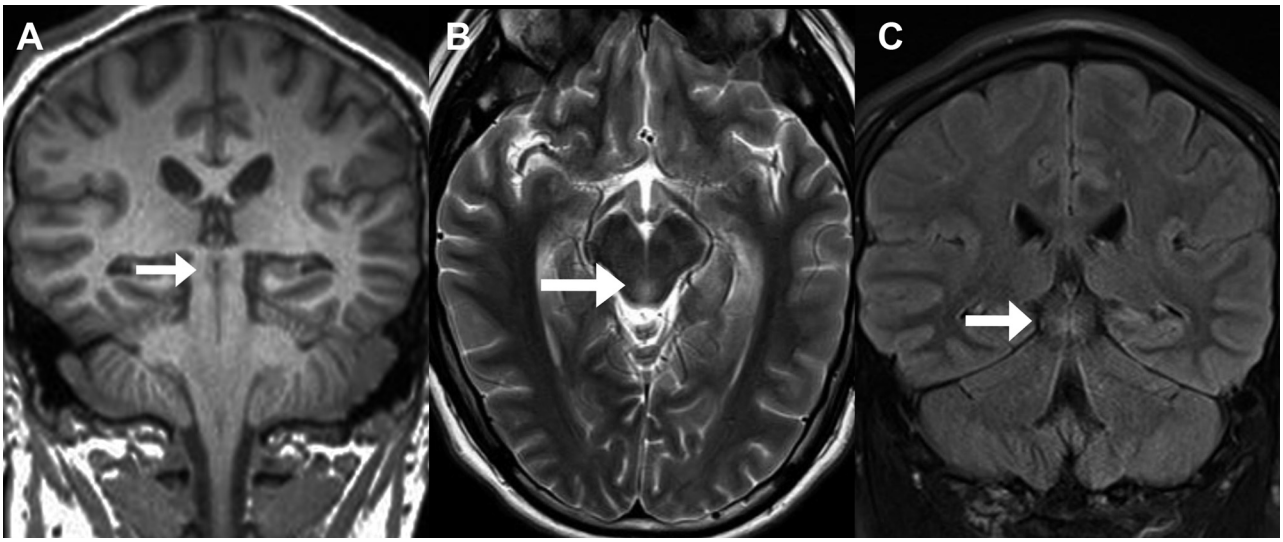

FIGURE 1.
Brain magnetic resonance imaging study at day 7 of illness demonstrating focal edema of the periaqueductal gray matter, as evidenced by hypointensity in an axial T1-weighted image (A) and hyperintensity in axial T2-weighted (B) and coronal T2 fluid-attenuated inversion recovery (C) images (white arrows).