CASE REPORT

ROHHAD Syndrome: The Girl who Forgets to Breathe

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Background: ROHHAD syndrome is an exceedingly rare cause of central hypoventilation. **Case characteristics:** A 7-year-old girl with ROHHAD syndrome who had central hypoventilation, rapid weight gain, multiple cardiac arrests and hyperprolactinemia. **Outcome:** She required prolonged and repeated ventilation, and finally died due to complications of ventilation. **Message:** ROHHAD Syndrome should be suspected in any child who presents with obesity, behavioral changes or autonomic instability following a neural crest tumor.

Keywords: *Autonomic instability,Hypercapnea, Hypoventilation, Obesity.*

Behavioral problems and obesity are commonly encountered conditions in the pediatric age group with a myriad of causes. However, when these occur together with unusual features such as hypoventilation, hypercapnea, dysautonomia and hypothalamic dysfunction, the constellation may represent a rare condition with an acronym of ROHHAD (Rapid onset obesity, Hypoventilation, Hypothalamic dysfunction, Autonomic dysfunction). We present a child with ganglioneuroblastoma and behavioral changes who was finally diagnosed to have ROHHAD syndrome.

CASE REPORT

A 7-year-old girl was first brought to us in 2010, at the age of 2 years, with complaints of unsteadiness of gait, jerky movements of the head and nystagmus. A paravertebral mass, that was confirmed on a CT-guided biopsy to be a ganglioneuroblastoma,was surgically removed and the child completed the course of chemotherapy.

A few months after completion of the chemotherapy, at 3½ years of age, the mother noticed a gradual change in the child's behavior. There was increasing aggressiveness, voracious appetite, and swearing and spitting at unfamiliar personnel. When her aggression reached the extent of causing harm to self and peers, the mother sought medical attention. A detailed psychiatric and psychological assessment was done. MRI brain, MIBG scan (for recurrence of ganglioneuroblastoma) and EEG were normal. The child was started on resperidone, which caused an extrapyramidal reaction, and was changed to quitiapin. There was history of schizophrenia in the father. At the age of 5 years, she was brought in an unconscious state following a suspected episode of a seizure with aspiration. The child was put on ventilatory support and treated for aspiration pneumonia. MRI brain showed evidence of recent bilateral hypoxic ischemic injury involving the basal ganglia, hippocampus and a few areas of the frontal, parietal and occipital lobes. In spite of an improving lung condition, alert mentation and spontaneous respiration, the child remained ventilator dependent and had severe retention of CO_2 when weaning was attempted. A tracheostomy was done in anticipation of prolonged ventilation. After about 4 months of ventilation, the child had an episode of accidental extubation following which there was an episode of cardiac arrest. This was followed by a second cardiac arrest within three weeks. Gradually, over a period of one and a half years, the child was successfully weaned off the ventilator but required BIPAP support due to persistent hypoventilation and CO_2 retention. During this time, the child also had a phase of rapid unexplained gain in weight and a voracious appetite prompting an endocrine workup. The child was discharged on nasal BIPAP with home pulse oximeter monitoring in October 2013.

In December 2013, the child was once again brought to the emergency department in a drowsy state with poor respiratory drive needing ventilation. A blood gas done as a part of the initial work up revealed severe CO_2 retention. Weaning and extubation after several days resulted in a third cardiac arrest, and she was put back on ventilatory support with tracheostomy. A sleep study done to evaluate hypoventilation as a cause of carbon-dioxide retention revealed obstructive sleep apnea. During the course in the PICU, the child developed episodes of polyuria (urine output 3-4 L/day or 6-8 mL/kg/hr) and serum sodium levels fluctuating between severe hypernatremia (sodium 189 meq/L) and

hyponatremia (sodium 115 meq/L). Child also had repeated episodes of hypothermia and unexplained bradycardia (heart rates dropping to as low as 35 per minute without any cardiorespiratory compromise).

The severe persistent hypoventilation, multiple cardiac arrests, unexplained electrolyte disturbances, episodes of diabetes insipidus and associated history of hyperphagia, behavioral disturbances and the neural crest tumour along with one phase of rapid weight gain led us to a suspicion of ROHHADs syndrome. Raised serum prolactin levels on two separate occasions confirmed the presence of a hypothalamic dysfunction. No *PHOX2B* gene mutations, deletions or duplications were detected in either the child or the mother. The child was given a trial with methylprednisolone followed by a course of rituximab. The child was initiated on BIPAP support on a need basis with monitoring of oxygen and CO_2 levels. She was initiated on cyclophosphamide and needed progressively less BIPAP support (once every few days) until a blocked tube (when she was hospitalized elsewhere) led to her sudden demise.

DISCUSSION

Though the symptom constellation of autonomic instability, hypoventilation, hypothalamic dysfunction and rapid onset obesity (Ondine's curse) was first described in 1965 [1]; late onset central hypoventilation with hypothalamic dysfunction [LO- CHS/HD] was described much later [2]. In 1997, Ize-ludlow, *et al.* [3] established rapid onset obesity as a major presentation in the majority of the patients with LO-CHS and proposed that the condition be renamed ROHHAD (Rapid onset obesity, Hypoventilation, Hypothalamic dysfunction and Autonomic dysfunction). The acronym was further extended to ROHHADNET to include neural crest tumors [4]. In 1994, North, *et al.* [5] proposed that LO-CHS/HD may be a paraneoplastic syndrome associated with neural crest tumours.

Our patient developed neuropsychiatric symptoms shortly after the completion of treatment for the ganglioneuroblastoma. Though documented, it is unusual for these patients to present initially with such symptoms [6]. Hyperphagia, leading to obesity, is often the earliest manifestation of this condition. Our patient presented with hyperphagia and rapid gain in weight but did not have obesity.

Respiratory manifestations that have been associated with LO-CHS/HD include alveolar hypoventilation, cardiopulmonary arrests, obstructive sleep apnea and reduced carbon dioxide ventilatory response. Our patient had many such events throughout her course in the hospital, including three cardiac arrests. The episodes of hyperthermia, hypothermia, cardiovascular instability and altered pain perception seen in our patient could be attributed to the autonomic dysfunction seen in this syndrome [3]. Interestingly, our patient never cried even once during her multiple procedures even with optimal sensorium. A negative *PHOX2B* mutation analysis excluded congenital central hypoventilation syndrome (Ondine's curse) [3]. The mutation analysis is critical since Ondine's curse can present anytime between the neonatal period to as late as adulthood [7]. Similarly, the elevated prolactin, electrolyte disturbances and the autonomic disturbances ruled out obstructive sleep apnea syndrome as the primary etiology for the hypoventilation, obesity and the cardiac arrests.

Though no cure has been reported so far, several therapies, including cyclophosphamide, have shown some promise [8]. Our patient showed reduction in the need for night time BIPAP (needing it once every 3 to 4 nights) in response to cyclophosphamide therapy.

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