Hirschsprung's Disease Associated With Ondine's Curse: Report of Three Cases and Review of the Literature

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● **The cases of three full-term infant girls with both Hirschsprung's disease (HD) and Ondine's curse (OC) are presented, and the relevant literature is reviewed. All three patients required endotracheal intubation and assisted ventilation during the first 24 hours of life because of respiratory distress. The diagnosis of HD was subsequently established at age 13, 16, and 20 days, respectively. The aganglionic segment was confined to the rectum in one case, extended to the splenic flexure of the colon in the second case, and involved the terminal ileum in the third. The definitive treatment (endorectal pull-through) was completed successfully in all three patients, and the postoperative follow-up period was 3 to 34 months. All of them presently have tracheostomies and are maintained on home ventilation. They tolerate being off the ventilator while awake, and have nearly normal bowel habits and growth curves. Two have bilateral ciliary ganglion dysfunction, and one has strabismus. Based on this review, the authors conclude the following. (1) The incidence of the HD associated with OC may be more common than is generally believed (1.8% of all their HD patients have OC). (2) OC should be suspected in any newborn with HD who requires assisted ventilation in the absence of major cardiopulmonary abnormalities. Likewise, HD should be ruled out in any OC case with gastrointestinal dysfunction. (3) Contrary to the previous impression from the literature, the combination of OC and HD should not be considered fatal, because most such patients can be managed successfully and have a reasonable quality of life. (4) The significant association of HD, OC, and ocular anomalies in all three of the authors' patients further substantiates the syndromic nature of this association, which should alert the clinician to perform regular screening for other possible neurocristopathies such as neuroblastoma.**
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ONDINE'S CURSE is the failure of automatic respiration during sleep. It is considered a subset of the larger disorder of central alveolar hypoventilation but is not synonymous with idiopathic or primary hypoventilation.[1] The name Ondine's curse (OC) derives from a German story of a sea nymph (Undine) whose husband jilted her for another female, and he was cursed for his unfaithfulness

with loss of automatic breathing, requiring him to remember to breathe continuously. When he finally fell asleep, he died.[2,3] The eponym "Ondine's curse" was applied for the first time in the medical literature to three patients who were thought to have suffered damage to the medullary carbon dioxide (CO_2) chemoreceptors as a result of surgery on the high cervical cord and brain stem.[3] The syndrome was initially described in adults[4] and later was recognized in infants.[5,6] It may be acquired as a result of neurological abnormalities[7] caused by encephalitis,[8,9] hypoxia-ischemia,[10] or surgical trauma.[3,11]

The diagnosis of OC is considered when there is hypoventilation resulting in progressive hypercarbia and hypoxemia during quiet sleep, which is reversible with assisted ventilation, associated with absent sensitivity to hypercarbia and hypoxia, and if there is absence of any primary cardiothoracic or neuromuscular pathology.[6] There should be significant differences between blood gas values of the awake state and those obtained during sleep.[12]

Congenital OC is considered a very rare phenomenon in infancy, with only about 50 reported cases.[13] Because Hirschsprung's disease (HD) is also relatively uncommon (estimated incidence of 0.02%),[14,15] the association of HD with OC is extremely rare; this was described for the first time by Haddad et al in 1978,[16] and then by others.[13,16-27] The prognosis for this association has been considered very poor.[20,22]

Herein we describe three new cases of HD associated with OC and review the relevant literature.

CASE REPORTS

Case 1

J.K., a 3,200-g full-term white girl was the product of an uncomplicated pregnancy and normal spontaneous vaginal delivery. Apgar scores were 4 and 8 at 1 minute and 5 minutes, respectively. The patient required endotracheal intubation and intermittent mechanical ventilation for recurrent episodes of apnea and bradycardia shortly after birth. The general physical examination showed no dysmorphic features. An eye examination showed strabismus. There were no obvious cardiopulmonary abnormalities. Seizures developed during the first few days, and mild hypotonia was noted. Results of a computed tomography (CT) scan of the brain, electrocardiogram, electromyograph, and brain stem auditory evoked response (BAER) test were normal. The diagnosis of OC was suspected because of unsuccessful weaning from the ventilator on repeated trials despite low ventilation settings and absence of cardiopulmonary anomalies. Polygraphic monitoring of the patient showed normal oxygen saturation when the patient was

maintained on continuous positive airway pressure (CPAP) while awake, but apnea hypercarbia and low oxygen saturation during sleep. The patient passed meconium spontaneously within the first 24 hours of life, but had one episode of bilious vomiting during the same period, followed by moderate abdominal distension. On the second day of life, a barium enema was interpretated as normal. Because of persistent abdominal distension, rectal suction biopsy was performed. This was diagnostic of HD. Laparotomy was performed 16 days of age, and frozen section biopsies confirmed the diagnosis of HD, with extension of the aganglionosis to 22 cm proximal to the ileocecal valve. Ileostomy was done in the ganglionated bowel. Tracheostomy was performed subsequently, when the need for long-term ventilation became obvious. The patient was maintained on parenteral nutrition for several weeks postoperatively, with gradual introduction of enteral feeding. She was discharged 25 weeks postoperatively and was maintained on home ventilation. At age 31 months, total colectomy and endorectal pull-through (ERPT) of the ileum were performed successfully. At present, the patient is 57 months old, she has five to seven formed bowel movements per day, is toilet trained, and has passed the normal developmental milestones. She tolerates being off the ventilator while awake, but still requires ventilatory support while sleeping.

Case 2

R.K., a 2,930-g full-term white girl was born to a 23-year-old primigravida who had an uncomplicated pregnancy and normal vaginal delivery at another hospital. The Apgar scores were 8 and 8 at 1 and 5 minutes, respectively. Shortly after birth, cyanosis developed, with occasional episodes of apnea. Two repeated doses of narcan were given; transient improvement was noted after the first dose but not after the second. At age 11 hours, mechanical ventilation was required because of the increased frequency of apneic episodes and bradycardia. The patient had no dysmorphic features, and her lungs and heart were normal on the physical examination. Mild hypotonia and unequal nonreactive pupils were noted. Results of a CT scan, ultrasound, and magnetic resonance imaging (MRI) of the brain, and a BAER test were normal. Repeated attempts at weaning the infant from the ventilator were unsuccessful. The patient passed meconium on the second day of life, but abdominal distension was observed. There was delayed evacuation of a gastrografin enema, which did not show a transitional zone. On day 16 of life, the patient was transferred to the C.S. Mott Children's Hospital, where clinical bedside sleep studies showed no respiratory drive and a rapidly increasing $PaCO_2$ and decreasing PaO_2. However, the patient tolerated CPAP very well while awake. A suction rectal biopsy performed on the same day showed HD. During laparotomy the next day, aganglionosis extending to the junction of the rectum and sigmoid colon was found, and a primary ERPT without colostomy was performed. A tracheostomy was also done at the same time. The patient did very well postoperatively except for one mild attack of enterocolitis 2 weeks after surgery, which was managed conservatively. At age 3.5 months, she required laparotomy and lysis of adhesion because of a bowel obstruction. Except for mild hypotonia, her developmental progress has been excellent. Her bowel pattern appears normal, with two to three bowel movements per day. She tolerates being off the respirator while awake. Results of urinary catecholamine tests, metaiodobenzylguanidine (MIBG) scans, and abdominal ultrasounds remain normal.

Case 3

L.A., a 3,510-g full-term white girl was born to a 25-year-old primigravida whose pregnancy was uncomplicated. A cesarean

section (CS) was required because of fetal distress. Apgar scores were 5 and 8 at 1 and 5 minutes, respectively. Intubation and assisted ventilation were required 4 hours after birth because of frequent apneic episodes. During examination, no dysmorphic features were noted, and the chest was normal to auscultation. Cardiac evaluation showed an atrial septal defect. The pupils were unequal, with minimal reaction to light. Results of MRI of the brain and a BAER test were normal, but an electroencephalogram showed generalized dysrhythmia, grade 1. The diagnosis of OC was made on the basis of polygraphic monitoring of the patient, both while awake and during sleep. The infant passed small amounts of meconium during the first 24 hours of life. At 6 days of age, the abdomen became markedly distended. A barium enema showed a transition zone at the splenic flexure of the colon, and the diagnosis of HD was confirmed by suction rectal biopsy. Both colostomy and tracheostomy were performed at another hospital. At 7 months of age, the child was referred to the C.S. Mott Children's Hospital for definitive care. The colostomy was taken down, and an ERPT was performed along with a descending colectomy. Presently, the patient has seven to 10 formed bowel movements per day, and tolerates being off the ventilator for variable periods while awake, but not while asleep. She has a normal growth curve and uses home ventilation (IP-10 ventilator).

LITERATURE REVIEW

Twenty six cases of congenital OC associated with HD (including our three patients) have been reported (Table 1). The gender distribution for 24 patients was equal (in two cases, sex was not reported). Of the 11 children for whom race was reported, eight were white and three were black. The pregnancy was uneventful in 17, associated with polyhydramnios in three, and not described in six cases. The method of delivery was vaginal in 15 cases, CS in five, and not described in six. Gestational age was reported in 23 cases; 20 infants were full-term, and three were premature. Birth weight for gestational age was normal for 14 of 17 infants. Good Apgar scores were reported for 11 of 15 infants, but deterioration of respiratory status necessitated endotracheal intubation and mechanical ventilation (from a few minutes to a few hours after birth) in 18 of 21 infants. Delayed intubation and assisted ventilation were reported in three cases (day 2, day 4, month 3).

The diagnosis of HD was established within the first week of life for 12 infants, and within the first 2 to 3 weeks of life for seven patients. (In seven cases, the age at diagnosis of HD was not reported.) The involvement of the aganglionic segment was as follows: in six, rectum or rectosigmoid (four girls, two boys); in two, descending colon (both girls); in 12, total colon aganglionosis with or without distal ileum involvement (six boys, four girls; sex was not reported for the other two); in four, mid or proximal jejunum (two boys, two girls); and in two, unknown. Definitive surgery (pull-through) was performed in eight patients. Both HD and OC occurred in two siblings and two half-siblings. In two cases, there was a family

Table 1. Data on 26 Patients With Congenital Ondine's Curse and Hirschsprung's Disease

Reference	Sex	Race	Pregnancy & Delivery	Gestational Age	Birth Weight (g)	Apgar Scores	Start of Assisted Ventilation	Age at Dx of HD	Extent of Aganglionic Segment	Surgical Intervention	Family History	Other Congenital Anomalies	Outcome
Haddad et al (1978)[16]	F	W	Normal	Full-term	2,900	?	Few hours	7 d	DC	Colostomy	Sibling affected	No	Died at 2 mo
Haddad et al (1978)[16]	F	W	CS	Full-term	2,580	7 & 9	3 h	5 d	TC	Ileostomy-closure	Sibling affected	No	Died at 5 mo
Haddad et al (1978)[16]	F	W	Normal	Full-term	3,175	? & 5	Minutes	?	TI	Duhamel	No	Ganglioneuro-blastoma	Died at 2 mo
Bower et al (1980)[17]	M	W	Normal	Full-term	3,400	6 & 0	First day	3 d	DS	Colostomy	?	Neuroblastoma	Died at 9 mo
Stern et al (1981)[18]	M	?	Normal	Full-term	3,830	4 & ?	First day	3 d	TI	Ileostomy-Rhebein PT	No	No	Died at 15 mo
Guilleminault et al (1982)[19]	M	?	Normal	Full-term	3,150	8 & 9	4 d	4 d	TC	Ileostomy	?	No	Died at 24 d
Guilleminault et al (1982)[19]	M	?	Normal	Full term	3,200	8 & 10	2 d	2 d	TC	Ileocolostomy	No	No	Alive at 24 mo, home ventilation
O'Dell et al (1987)[20]	M	B	Normal	Full-term	2,400	2 & 6	At birth	21 d	TI	Ileostomy	?	No	Alive at 5 mo
Poceta et al (1987)[21]	M	W	Polyhy-dramnios	Full-term	2,500	6 & 8	First hour	14 d	PJ	Exploration	?	Ciliary ganglion dysfunction	Died at 40 d
Poceta et al (1987)[21]	F	?	Normal	Full-term	?	2 & 6	At birth	?	TC	Ileostomy	?	Abnormal BAER	Died at 30 mo
Roshkow et al (1988)[22]	M	?	?	Full-term	?	?	?	?	MJ	?	No	No	Died at 3 mo
Roshkow et al (1988)[22]	M	?	?	34 wk	?	?	?	?	TI	?	2 stillborn siblings	No	Alive at 13 mo, at hospital
Roshkow et al (1988)[22]	M	?	?	Full-term	?	?	?	?	PJ	?	?	No	Died at 15 d
Wesse-Mayer et al (1988)[23]	?	?	?	?	?	?	?	?	TC ?	?	?	?	?
Wesse-Mayer et al (1988)[23]	?	?	?	?	?	?	?	?	TC ?	?	?	?	?
Hamilton et al (1989)[24]	F	B	CS	Full-term	2,440	?	6 h	7 d	R	Colostomy-closure	Half-sibling affected	Esotropia	Alive at 54 mo, at hospital
Hamilton et al (1989)[24]	M	B	CS	Full-term	3,030	?	At birth	4 d	R	Colostomy-closure	Half-sibling affected	No	Alive at 30 mo, at hospital
Minutillo et al (1989)[13]	F	?	Normal	Full-term	3,060	6 & 7	8 h	3 d	TI	Ileostomy	No	Facial dysmorphic features	Died at 19 d
Gaisie (1989)[25]	M	?	Normal	Full-term	3,400	Good	At birth	5 d	?	Colostomy	?	Neuroblastoma	Died at 7.5 mo
Fodstad et al (1990)[26]	F	?	Normal	Full-term	?	?	3 mo	3 mo	R	Colostomy	No	No	Alive, diaphragm pacing
Fodstad et al (1990)[26]	F	?	?	?	?	?	At birth	1 mo	RS	Colostomy	No	No	Alive, diaphragm pacing
Fodstad et al (1990)[26]	M	?	Polyhy-dramnios	36 wk	2,430	?	First day	3 d	PJ	Ileostomy	No	No	Died at 1 mo
Mukhoopadhyay et al (1990)[27]	F	?	Polyhy-dramnios	35 wk	?	2 & 7	At birth	Few days	?	Colostomy	?	Ciliary ganglion dysfunction	Alive at 36 mo
Present series (1993)	F	W	Normal	Full-term	3,200	2 & 8	Few hours	13 d	TI	Ileostomy-ERPT	No	Strabismus	Alive at 57 mo, home ventilation
Present series (1993)	F	W	Normal	Full-term	2,900	8 & 8	11 h	16 d	R	Primary ERPT	No	Ciliary ganglion dysfunction	Alive at 17 mo, home ventilation
Present series (1993)	F	W	CS	Full-term	3,150	5 & 8	4 h	20 d	SF	Colostomy-ERPT	No	Ciliary ganglion dysfunction, ASD	Alive at 7 mo, home ventilation

Abbreviations: ASD, atrial septal defect; B, black; CS, cesarean section; DC, descending colon; ERPT, endorectal pull-through; MJ, midjejunum; PJ, proximal jejunum; R, rectum; RS, rectosigmoid; SF, splenic flexure; TC, total colonic; TI, terminal ileum; W, white; ?, unknown.

history of a previous still birth in which the cause was unknown. The most common associated anomalies were ocular (5), neuroblastoma or ganglioneuroblastoma (3), cardiac (2), deafness (1), facial dysmorphic features (1), and cerebral arteriovenous malformation (1). Thirteen patients died, and 11 are alive. No specific brain stem focal pathology was noted in 10 cases for which autopsies were performed.

DISCUSSION

Automatic respiration is stimulated by a rhythmic discharge of the respiratory center neurons in the medulla (dorsomedially in the nucleus tractus solitarus, and ventrolaterally near the nucleus retroambigous), and regulated by chemical stimuli through both central and peripheral chemoreceptors as well as nonchemical stimuli such as pulmonary baroreceptors.[1] Central chemoreceptors respond to cerebrospinal fluid hydrogen ion changes, determined predominantly by changes in $Paco_2$,[28] whereas peripheral receptors respond mainly to Pao_2 and pH changes.[29] A CO_2 ventilatory response is not necessary in the infant at rest, except during quiet sleep.[30] Awake ventilation is maintained either by a hypoxemic stimulus or by conscious control.[31] Neural output from nonchemoreceptor sources may be sufficient to drive ventilation while awake and during rapid eye movement (REM) sleep, but is absent or becomes inhibited in the quiet sleep state.[30] Malfunction of the central chemoreceptors results in loss of automatic respiration during quiet sleep, and this represents the syndrome of OC.[24]

In 10 cases with known autopsy findings, neither specific CNS pathology nor focal lesions in the brain stem were found. Although hypothalamic focal disease,[32] absence of the external arcuate nucleus,[33] and decreased density of neurons and myelinated nerve fibers in the respiratory center[34] have been found in single cases, it is generally accepted that congenital OC is not associated with major CNS abnormalities.[35] Liu et al[36] suggested the presence of such abnormalities at the molecular level. CT scans, MRI, and cranial ultrasound examinations of the brain have not shown specific brain stem pathology. Wesse-Mayer et al[23] postulated that the lesions may be beyond the resolution of current imaging modalities. Abnormal BAER findings were reported in two of the five cases with known results. Similar findings have been reported previously.[37,38]

Our three cases have been seen within the last 5 years and represent 1.8% of all HD cases treated since 1974 (170 patients) at our institution. The incidence of HD is 43% (three of seven) among all cases of congenital OC on home ventilation, managed at our hospital. These 26 cases represent a 50% incidence of HD among all published congenital OC cases. These data clearly establish the association of OC and HD, which may be caused by a primary defect of the stem serotonergic nerve cells, both in the brain stem and the alimentary tract,[16] or may result from a neural crest migrational abnormality.[17]

Congenital OC has been reported in association with congenital neuroblastoma[16,39] and ganglioneuroblastoma.[40] Boland[41] applied the term "neurocristopathy" to lesions resulting from maldevelopment of the neural crest tissues, such as pheochromocytoma, medullary carcinoma of the thyroid, carcinoid tumors, and HD. Neuroblastoma and ganglioneuroblastoma were diagnosed at birth in three patients (11.5%). Ciliary ganglion dysfunction and abnormal ocular movements were present in five children (19%) and congenital deafness in one (4%).[42] These associated anomalies support the concept of a common embryologic neural crest abnormality.[39]

The gender distribution was equal, which can be explained by the high percentage of long-segment and total colonic aganglionosis with or without proximal small intestinal extension. The white:black ratio was 2.6:1 among 11 patients. An uneventful pregnancy was noted in 85%, and a normal vaginal delivery was described in 75% of cases with a known pregnancy/delivery history. Most of the infants (87%) were full-term, with a birth weight appropriate for gestational age. Good Apgar scores were reported in 69% of the cases, but endotracheal intubation and assisted ventilation were required within the first 24 hours after birth in almost all newborns. There was no significant delay in the diagnosis of HD in most patients. The aganglionic segment was classic (rectum or rectosigmoid) in only 25% of these cases, in contrast to the general population of patients with HD (66.3% to 77.7%).[43,44] Obviously, the association between OC and HD increases as the proximal extension of aganglionosis increases. Two siblings and two half-siblings (15.4%) were among the 26 patients. Haddad et al[16] suggested an autosomal recessive inheritance of HD-associated OC; however, Badner et al[15] found a dominant gene inheritance in long-segment HD. A recessive gene with very low penetrance appears to be the most likely pattern of inheritance for standard HD.[15]

Many drugs have been used in therapeutic trials for the management of OC, with limited or no success.[45,46] Long-term assisted mechanical ventilation[47] or diaphragmatic pacing are the current preferred methods of treatment for OC. Diaphragmatic pacing was reported in two cases in this study, and resulted in successful weaning from mechanical ventilation.[26] In

several other reported cases of OC without HD, results were similar.[5,40,48] Diaphragmatic pacing appears to be effective in reducing pulmonary vascular resistance and pulmonary hypertension,[49] but its long-term use can lead to loss of phrenic nerve conductivity.[50]

The outcome of HD-associated OC was very poor in the earlier cases in this collective review. Death usually resulted from repeated bouts of pulmonary infection or heart failure secondary to pulmonary hypertension caused by hypoxemia.[6]

Our three cases had some unique characteristics. They represent the spectrum of HD (standard, long-segment involving the descending colon, and total colonic aganglionosis with distal ileal involvement). Ocular abnormalities were observed in all. The ERPT procedure was successful in all three children, with nearly normal bowel habits noted during at follow-up. Presently these patients are being managed successfully with home ventilation, and they have reached normal developmental milestones.

This review of our three cases and those in the literature clearly indicates that a high index of suspicion will result in the diagnosis of more cases of neurocristopathies, with various combinations.

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