Congenital Failure of Autonomic Control

Alternative Names
Ondine Curse, Congenital
Central Hypoventilation Syndrome, Congenital
CCHS
Ondine-Hirschsprung Disease
OHD
CCHS with Hirschsprung Disease
Haddad Syndrome

WHO International Classification of Diseases
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified

OMIM Number
209880

Mode of Inheritance
Autosomal Recessive vs. Dominant with Reduced Penetrance (or Paternal Gonadal Mosaicism)

Gene Map Locus
20q13.2-q13.3, 12q22-q23, 11p13, 10q11.2, 5p13.1-p12, 4p12

Description
Congenital failure of autonomic control is a life-threatening disorder characterized by persistent hypoventilation, most pronounced during sleep, with relative insensitivity to hypercarbia and a lesser insensitivity to hypoxia, in the absence of other abnormalities of the cardiorespiratory system, beginning in the neonatal period and requiring life-long ventilatory assistance. Changes in the integration of afferent inputs from central and peripheral chemoreceptors in the brainstem are the most likely disease mechanisms.

It is thought to originate in a failure of migration of neural crest derived precursor cells, although this is controversial and a hostile gut microenvironment may also contribute.

The association of congenital failure of autonomic control with congenital central hypoventilation syndrome was first reported in 1978. This syndrome is rare; only about 50 cases have been reported worldwide. The disease complex is called neurocristopathy, that is, aberrant phenotypes arising from a defect of migration or differentiation of neural crest cells.

Molecular Genetics
Congenital failure of autonomic control can be caused by mutation in the paired-like homeobox 2B (PHOX2B) gene as well as in several other genes, including RET, GDNF, EDN3, and BDNF. PHOX2B is the major disease-causing gene, mutated in half to two thirds of patients with congenital failure of autonomic control. Its coding region consists of 945 base pairs allocated in three exons, yielding a homeodomain protein of 314 amino acid residues. The DNA-associated protein encoded by the PHOX2B gene is a member of the paired family of homeobox proteins localized to the nucleus, functioning as a transcription factor involved in the development of several major noradrenergic neuron populations and the determination of neurotransmitter phenotype.

Epidemiology in the Arab World

Saudi Arabia
Mansoor and Zahrani (2002) analyzed 27 consecutive cases of endoscopic colonic biopsies and surgical colectomy specimens of both male and female cases who were received for investigation of ganglion cells for the Hirschsprung’s disease and related disorders. In their study, Mansoor and Zahrani (2002) looked for only three symptoms and all the 27 patients
presented with constipation, 15 (55.5%) patients had abdominal distension and no patient presented with diarrhea. Mansoor and Zahrani (2002) suggested that a wider population study for the genetic factors of this frequent congenital disease is highly recommended in the Saudi population.

Khan et al. (2003) determined the incidence of Hirschsprung's disease in children who presented with constipation to a specialist paediatric surgical unit. During a 5-year period, 355 rectal biopsies were performed on 182 neonates, infants and children presenting with chronic constipation or intestinal obstruction: 25 (14%) were diagnosed with Hirschsprung's disease.

United Arab Emirates
Fogstad et al. (1989) described three patients with the combination of congenital failure of autonomic control and Hirschsprung's disease. Case one, a male neonate had total colonic aganglionosis, a hypertrophied nerve trunk with increased esterase activity, and apnoea requiring endotracheal incubation and ventilation. The baby died aged one month from the combination of enterocolitis, septicaemia and pneumonia. Post-mortem examination revealed patchy bronchopneumonia and generalized cholestasis of the liver. Case two, a female baby, had nocturnal perspiration, sudden awakening with respiratory difficulties and aganglionosis at three months of age, and upper respiratory tract infection followed by apnoea lasting 10 to 20 seconds with hypoxia and hypercapnia, seizures, cardiac arrest, and oedema at 20 months of age. Case three, a female baby was diagnosed shortly after birth to have congenital failure of autonomic control and Hirschsprung's disease. The baby had pulmonary complications and total colonic aganglionosis. During infancy she had epileptic seizures and was hypertensive with generalized oedema. In case two and three, at the ages of two and six years, respectively, phrenic nerve stimulators were implanted. Both females remained independent of nocturnal mechanical ventilation two and three years after the commencement of diaphragm pacing. Fogstad and colleges (1989) concluded that patients with congenital failure of autonomic control combined with Hirschsprung's disease, who survive neonatal period should be considered candidates for electrophrenic respiration as an alternative or even treatment of choice for restoring normal breathing and improving equality of life.

Al Talabani et al. (1998) studied the pattern of major congenital malformations in 24,233 consecutive live and stillbirth at Corniche hospital, which is the only maternity hospital in Abu Dhabi, between January 1992 and January 1995. A total of 401 babies (16.6/1,000), including 289 Arabs, were seen with major malformation. Sporadic conditions accounted for 26% of the cases. In their study, Al Talabani et al. (1998) observed one case of congenital failure of autonomic control in a family from the United Arab Emirates. Recurrence was not reported in other members of the family. Al Talabani et al. (1998) concluded that their study was very close to representing the true incidence of congenital abnormalities in the whole United Arab Emirates, as they investigated over 98% of deliveries in Abu Dhabi, the capital of United Arab Emirates.

References

Contributors
Sarah Al-Haj Ali: 2.6.2005
Ghazi O. Tadmouri: 20.2.2005