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Ondine-Hirschsprung syndrome (Haddad syndrome)

Further delineation in two cases and review of the literature

A. Verloes[1], C. Elmer[2], D. Lacombe[3], C. Heinrichs[4], E. Rebuffat[4], J. L. Demarquez[3], A. Moncla[5], and E. Adam[6]

[1] Centre of Human Genetics, Liège University, Pathologie B23, C. H. U. Sart Tilman, B-4000 Liège, Belgium
[2] Centre of Human Genetics, Free University of Brussels, Belgium
[3] Clinic of Paediatrics and Medical Genetics, and Paediatric Intensive care Unit, Children Hospital, Bordeaux, France
[4] "Reine Fabiola" University Hospital for Children, Brussels, Belgium
[5] Centre of Genetics, La Timone Hospital, Marseille, France
[6] Neonatal intensive Care Unit, University Hospital Tivoli, La Louvière, Belgium

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Abstract. Two unrelated children with congenital central hypoventilation syndrome (CCHS-Ondine syndrome) and long segment Hirschsprung disease are reported. Patient 1, a girl, is still alive at 3 years. Patient 2, a boy, died of viral pneumonia at 5.5 years. Continuous mechanical ventilation was necessary for months and those children could never be weaned from the respirator during sleep. Seventeen cases of this complex neurocristopathy are reviewed. Only six children (including our cases) survived beyond 2 years of age. Hypotonia, delay in developmental milestones or epilepsy were frequently observed. Ventilator dependency does not improve with time. Multifocal congenital neuroblastoma occurred in two children. Aetiology is unknown.

Key words: Hirschsprung disease – Neurochristopathy – Ondine's curse – Review

Introduction

Congenital central hypoventilation syndrome (CCHS) is an uncommon defect in the regulation of breathing leading to life-threatening hypoxia in infancy. The cause is a still unknown defect in the feedback control of ventilation. We report on two children with CCHS complicated by Hirschsprung disease and review 17 previous cases.

Case reports

Case 1

This girl was born at 38 weeks of a pregnancy complicated by preeclampsy. Birth weight was 2810 g, birth length was 50 cm and occipitofrontal circumference was 34.5 cm. Apgar score was 8/ 9. She was the only child of non consanguineous parents in good health, both aged 28 at the time of birth. Family history was unremarkable. Intubation was necessary at 15 h because of apnoeas and cyanosis. Weaning from the ventilator was impossible. Almost permanent ventilation via tracheostomy was required during the 1st year. After 6 months, she could tolerate short periods of unsupported breathing. At 3.5 years, she still required ventilation at home during sleep. She suffered chronic respiratory tract infections. Chronic hypercapnia (pCO_2 between 50 and 65 Torr) and intermittent hypoxia when awake were recorded. She was resuscitated on three occasions because of acute asphyxic episodes with concomitant convulsions and coma. Recurrent intestinal obstructions were treated by left colostomy at 2 months of age. The aganglionic colic segment extended to midtransverse colon. Multiple hypoglycaemic accidents (blood glucose <25 mg/dl) without acidosis or ketonuria were recorded, mostly in preprandial period. No hepatomegaly was observed. Hyperinsulinism, growth hormone or cortisol deficiencies and other endocrine dysfunctions were excluded and metabolic screening (aminoacids, organic acids, lactate, pyruvate, carnitine and acylcarnitines) was not contributive. Liver biopsy was not performed. Physical development was slow. Height was below -3 SD, weight was at -1SD and head circumference at 25th percentile. She had a square, flat face and a slight hypertelorism. Developmental milestones were delayed: she sat at 9 months and walked at 27 months. Language remained poor. CT scan disclosed a general cortical atrophy predominating in the frontal areas with diffusely widened sulci and slightly enlarged ventricles. EEG showed an irritative pattern which was attributed to postasphyxic lesions. MRI was not done.

Case 2

This boy was born at term by caesarean section. Birth weight was 2950 g, birth length was 50 cm and head circumference was 36 cm. Apgar score was 4/8. He was the first child of non consanguineous healthy parents, aged respectively 23 and 21 at the time of birth. His younger sister was healthy. Family history was unremarkable. At 4 days, he was admitted to a paediatric intensive care unit for bowel obstruction due to total colic aganglionosis. Colectomy and colostomy were performed. After surgery the child could not be weaned from the ventilator. Independence from ventilator when a wake was possible after some months, but never for night and nap. Gluten enteropathy was diagnosed at 15 months. Severe gastro-oesophageal reflux required Nissen fundoplasty at 18 months. Subcontinuous feeding with semi-elementary, hypo-allergenic diet, administered via gastrostomy, was still required at 5 years. At this

Correspondence to: A. Verloes

Abbreviation: CCHS = congenital central hypoventilation syndrome

Table 1. Clinical features of Ondine-Hirschsprung syndrome

Clinical feature	Previous reports
Number of cases	17
Birth weight (mean ± 2SD)	2921 g ± 724 ($n = 11$)
Fetal suffering/low Apgar	6/11
Sex	10 M – 5 F
Hirschsprung disease	17/17
with ileal/jejunal involement	7/15
colic, total	3/15
colic, partial	5/15
Death before 6 months	8/17
Death after 6 months	2/17
Survival > 23 months	4/17
Abnormal neurological status	4/ 8
Neuroblastoma	2/17

time, weight and height were at −4 SD. The patient was not dysmorphic. Psychomotor development was slightly retarded. He walked at 28 months. At 5 years, he spoke fluently and attended maternal school. CT scan was normal. EEG was considered slow for age. He died of an interstitial respiratory syncitial virus pneumopathy at 5.5 years of age.

Discussion

The neural control of respiration is complex and involves multiple nuclei located both in the ventral and dorsal areas of the brainstem. These nuclei are influenced by a neuronal rhythm generation centre, upper structures lying into the pons, and afferent projections of the lung mechanoreceptors and of the ventral medullary, carotidian and aortic chemoreceptors. Severinghaus and Mitchell [14] imaginatively described as "Ondine's curse" a syndrome of central hypoventilation (Ondine syndrome), the result of an inoperative feedback from the hypoxic-hypercapnic chemoreceptors located into the ventrolateral area of the medulla. This defect seems responsible for the absence of ventilatory response when pCO_2 rises. Most cases of Ondine syndrome were observed in adults and some are clearly due to acquired diseases such as encephalitis. About 40 children with CCHS have been reported [2, 11, 16, 18]. CCHS is characterised by pathological hypoventilation at least during NREM sleep. In some children, primary or acquired lesions of the brain were observed but neurophysiological and neuropathological investigations were inconclusive in most patients [8]. Generally, cases are sporadic but a probably dominantly inherited form has been reported [3].

A clinically consistent subset of patients with CCHS, first delineated by Haddad et al. [5], is characterised by an association with colon aganglionosis. Table 1 summarises the clinical data of 17 patients with similar clinical features [1, 4–6, 9, 10, 12, 13, 15, 17]. All children required mechanical ventilation and none could be weaned from it for sleep. Diaphragmatic pacing was attempted in some cases but with little success. Dependency upon mechanical ventilation does not persist, in contrast to isolated CCHS which shows a better prognosis and even sometimes a spontaneous recovery [18]. Hypotonia, delay in developmental milestones or epilepsy observed in several children were very likely secondary to chronic or acute hypoxia. Only six patients (including our cases) survived beyond 2 years of age. Most infants died from respiratory-related problems (including cor pulmonale and overwhelming infections) or from surgical complications. Multifocal congenital neuroblastoma occurred in two children. Minutillo et al. [9] observed abnormal corneal and pupillary reflexes and facial dysmorphism: antimongoloid slant, triangular shaped mouth and small nose. Our patients did show similar features.

Hirschsprung disease is commonly considered as resulting from an abnormal migration of the neural crest cells from the first somitic levels. It has been suggested that a "permissive environment" depending on the gut itself controls the migration of the ganglionic cells [7]. Sympathetic nervous system and adrenal medulla differentiate from neural crest along the spinal cord. The concept of an association between aganglionosis and ganglioneuroblastoma seems possible, although the core mechanism of this combined neurocristopathy which links abnormal control of the migration in one class of cells and abnormal differentiation and tumorigenesis in another cell line remains unknown. The common point between those neurocristopathies and CCHS is not elucidated. The chromaffin cells of the carotid bodies, which stem from the neural crest, do not seem involved in the pathogenesis [4, 5]. A dysfunction of the medullary chemoreceptors (which are not of neural crest origin) or a more complex defect in the brainstem regulation of the respiration is likely. Haddad et al. [5] postulated that the primary defect lies in an abnormal development of serotoninergic stem cells present in myenteric plexi and in areas of the brainstem close to the centres involved with the regulation of respiration.

Two familial cases of Ondine-Hirschsprung syndrome are known, affecting two sisters [5] and two half-sibs with the same unaffected father [9]. This could indicate a multigenic predisposition, or perhaps, true mendelian inheritance, e.g. dominant inheritance with reduced penetrance. Further case reports are needed to solve this problem. Incidence of the disease is impossible to estimate. No other cases were ascertained in genetic centres in Belgium or France, and no similar cases were found in a retrospective study of 250 cases of Hirschsprung disease (A. Toutain, Tours, France, personal communication).

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Note added in proof

Weese-Mayer [1] recently reported a collaborative study of 37 families with CCHS: 32 cases were fully investigated (but not individually described); familial data were collected in 12 others. There were 6 (unreported?) cases with Ondine-Hirschsprung syndrome, including 2 sibs (brother and sister). No recurrence was observed in the families with isolated CCHS, giving further argument for the delineation of Ondine-Hirschsprung syndrome as a distinct entity with high recurrence risk and possible genetic etiology.

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