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Ha Trang, Michel Dehan, François Beaufils, Isabelle Zaccaria, Jeanne Amiel and Claude Gaultier

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The French Congenital Central Hypoventilation Syndrome Registry*

General Data, Phenotype, and Genotype

Ha Trang, MD, PhD; Michel Dehan, MD; François Beaufils, MD; Isabelle Zaccaria, MD; Jeanne Amiel, MD; and Claude Gaultier, MD, PhD; and the French CCHS Working Group†

Objective: **To analyze the main clinical features, genetic mutations, and outcomes of patients of the French Congenital Central Hypoventilation Syndrome (CCHS) Registry.**
Design: **A country-wide cohort established throughout a long-term multicenter effort.**
Patients: **Seventy French patients with CCHS (29 male patients and 41 female patients).**
Methods: **The following items were analyzed: the most important moments of the disease course; the main clinical characteristics; associated pathologic conditions; management; clinical outcome; and genetic mutations.**
Results: **An average of four new cases of CCHS per year was observed in the last 5 years. Thus, the incidence may be estimated to be 1 per 200,000 live births in France. The median age at diagnosis was 3.5 months (range, 0.5 to 15 months) before 1995 and < 2 weeks in the last 5 years ($p = 0.01$). CCHS occurred in isolation in 58 of 70 patients. In the remainder, it was associated with Hirschsprung disease (HSCR) [nine patients], Hirschsprung and neural crest tumor (two patients), and growth hormone deficiency (one patient). Among the 50 patients who lived beyond 1 year of age, all but one received nighttime ventilation, with 10 of them (20%) receiving it noninvasively. Three patients (6%) required daytime ventilatory support in addition to nighttime ventilation. The overall mortality rate was 38% (95% confidence interval [CI], 27 to 49%). The median age at death was 3 months (range, 0.4 months to 21 years). The 2-year mortality rate was greater in male patients than in female patients ($p = 0.02$; relative risk [RR], 2.71; 95% CI, 1.14 to 6.47) but was not affected by HSCR ($p = 0.93$; RR, 0.95; 95% CI, 0.28 to 3.2). The 43 patients who are currently alive (11 men; sex ratio, 0.4) have a mean age of 9 years (range, 2 months to 27 years). Among the 34 patients tested thus far, heterozygous mutations of the paired-like homeobox gene 2B (*PHOX2B*) gene were found in 31 patients (91%).**
Conclusion: **Our four major findings are the extreme rarity of CCHS, the improved recognition over time, the lack of effect of HSCR on the mortality rate, and the high frequency of *PHOX2B* mutations.** ***(CHEST 2005; 127:72–79)***

Key words: central alveolar hypoventilation syndrome; mortality; registry

Abbreviations: CCHS = congenital central hypoventilation syndrome; CI = confidence interval; *HASH-1* = human *achaete-scute* homologue 1; HSCR = Hirschsprung disease; *PHOX2B* = paired-like homeobox gene 2B; RR = relative risk

Idiopathic congenital central hypoventilation syndrome (CCHS) is a rare condition that is characterized by abnormal autonomic control of breathing resulting in alveolar hypoventilation that is most marked during slow-wave sleep.[1–3] The initial description was reported by Mellins et al[1] in 1970. The association of CCHS and Hirschsprung disease

*From the Service de Physiologie (Drs. Trang and Gaultier), INSERM E-9935, Hôpital Robert Debré, Assistance Publique-Hôpitaux de Paris, Université Paris 7, Paris, France; Service de Réanimation Néonatale (Dr. Dehan), Hôpital Antoine Béclère, Clamart, France; Service de Réanimation Pédiatrique (Dr. Beaufils) and the Unité d'Epidémiologie Clinique (Dr. Zaccaria), Hôpital Robert Debré, Paris, France; and the Département de Génétique (Dr. Amiel), INSERM U-393, Hôpital Necker Enfants Malades, Paris, France.
†A list of participants in the French CCHS Working Group is located in the Appendix.

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Correspondence to: Ha Trang, MD, PhD, Service de Physiologie, Hôpital Robert Debré, 48 Blvd Serurier, 75019 Paris, France; e-mail: ha.trang@rdb.ap-hop-paris.fr

(HSCR) was first reported in 1978 by Haddad et al,[4] and was found to be frequently present.[5–7] Only recently, the heterozygous mutations of the paired-like homeobox gene 2B (*PHOX2B*) were first identified in patients with CCHS by Amiel et al.[8]

In France until the early 1990s, CCHS was an orphan disease that was misdiagnosed and mismanaged. Little was known about the number of patients with the disease. No physician had seen more than one or two children with CCHS. No recommended procedure existed for its management, and no research program was targeted at the disease. Beginning in 1996, collaborative efforts have been made to create a clinical and research center devoted to CCHS with full support from patients and families. The French family association was founded in 1998. A Web site that is coadministered by physicians and families became available in 2000.

This article describes the methods by which the French CCHS Registry has been established throughout a long-term multicenter effort, and collates the information of 70 French patients with CCHS. Our objectives were to estimate the incidence of CCHS in our country and to analyze the clinical characteristics, genotype, management, and outcome of this rare, congenital respiratory condition in a unique, country-wide cohort.

Materials and Methods

In 1993, we initiated a national survey among neonatal and pediatric ICUs, as well as anesthesia care units, to identify the patients in whom CCHS has been diagnosed. Fifty-eight postal questionnaires were sent, and 45 responses obtained. One of us (H.T.) reviewed all medical records and sleep tracings whenever they were available. This allowed us to identify 32 patients who fulfilled the criteria for CCHS.[1] In 1996, the number of recorded patients was 34. An update was performed yearly using telephone interviews of neonatal and pediatric intensivists.

Since 1996, a CCHS center, based in Paris, France, has performed the diagnosis, treatment, and follow-up of CCHS patients. To date, 47 patients have been evaluated in our center. Twelve patients were born before 1996 and were investigated at various ages for the first time by our team (Department of Physiology, Trousseau Hospital, then Antoine Béclère Hospital, Paris, France), 21 others were born after 1996 and were investigated at birth, and the remaining 14 who were identified by the national survey cited above came into our center for the first time as older children. All patients underwent a complete investigation to confirm CCHS disease and were subsequently followed up. Our criteria for CCHS included the following: (1) persistent central alveolar hypoventilation during sleep detected by polysomnography while the patient spontaneously breathed room air; (2) no primary lung, neuromuscular, cardiac, or brainstem abnormalities that could explain the hypoventilation[2,3]; (3) and absent or markedly reduced hypercapnic ventilatory responses.[2]

In addition, we reviewed the medical records of 23 other patients in whom CCHS was diagnosed based on recordings of transcutaneous Po_2 and Pco_2 measurements or sleep studies during spontaneous ventilation. Hypercapnic ventilatory responses were not available. These patients, who have been identified by the 1993 national survey that is updated yearly, were not investigated in our center. Fifteen of them died before 1995, 3 died after 1995, and 5 were alive.

All patients and parents gave consent to our accessing the information on them being held by the Registry staff. To date, the French CCHS Registry currently includes 70 French patients (Table 1). For the purpose of this study, the following four groups of items were analyzed: (1) clinical characteristics (*ie*, gender and date of birth), the most important moments in the course of the disease (*ie*, age at onset of symptoms, age at diagnosis, age at tracheostomy, age at initial hospital discharge, and age at transition to noninvasive ventilation whenever this option was chosen), associated pathologic conditions (*ie*, HSCR and neural crest tumors, based on histology of surgery or biopsy specimens), and growth hormone deficiency (identified by endocrine test results); (2) clinical outcome; (3) respiratory care and progress; and (4) genetic mutations (*ie*, the presence or absence of mutations in the *PHOX2B* gene or in other candidate genes involved in the early development of the autonomous nervous system (*ie*, human *achaete-scute* homologue 1 [*HASH-1*], glial cell-derived neurotrophic factor, neurturin, receptor tyrosine kinase, endothelin-B receptor, endothelin-3, brain-derived neurotrophic factor, and respiratory neuron homeobox).

Statistical Analysis

Descriptive statistics were used to analyze the demographic variables. Frequencies and percentages were presented for categoric variables. Median and extreme values were presented for continuous variables. Patient characteristics were compared by use of the Mann-Whitney *U* test and the Pearson χ^2 test for proportions. Survival curves from birth were computed using the Kaplan-Meier estimate and were compared with the use of the log-rank test. Relative risks (RRs) and their 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model. All tests were two-sided. A p value of < 0.05 was considered to be statistically significant. Statistical analyses were performed using statistical software (SPSS, version 10.1; SPSS; Chicago, IL; and SAS, version 8.02; SAS Institute; Cary, NC).

Table 1—*Source of Patients Included in the French CCHS Registry*

Patient Source	Patients, No.
1980–1995	
Trousseau Hospital then Béclère Hospital	12
1993 national survey (and yearly updates)	22*
Total	34
1996–2003	
CCHS Center (Robert Debré Hospital, Paris)	47
Follow-up	12
Investigated at birth and followed up	21
Investigated for first time as older children and followed up	14
Data review	23
Dead before 1995	15
Dead after 1995	3
Alive	5
Total	70

*Fifteen patients died before 1995.

Results

The 70 French CCHS patients consisted of 29 male patients and 41 female patients (sex ratio, 0.7). All but two patients were born as a result of spontaneous pregnancies. There were one drug-induced pregnancy (clomiphene citrate) and one *in vitro* fertilization using the biological father's sperm (not using intracytoplasmic sperm injection). The eldest patient was born in 1976. There was an average of four new CCHS cases per year in the last 5 years. This number was nearly twice as high as that of the early 1980s.

Associated Pathologic Conditions

CCHS was present in one pair of male-female siblings and in one pair of monozygotic female twins. CCHS occurred in isolation in 58 patients (83%) and was associated with other conditions in the other 12 patients (17%).

Among these 12 patients, 11 (6 male patients and 5 female patients; sex ratio, 1.2; 16% of CCHS patients) had associated HSCR. HSCR involved a long segment in eight patients (total colonic aganglionosis, six patients; left colon, two patients) and a short segment (rectum and/or sigmoid colon) in two patients, whereas the affected length was unknown in one patient. Thus, the percentage of patients with long-segment HSCR was 80%. Furthermore, the associations among CCHS, HSCR, and neural crest tumors was observed in two patients (3% of all CCHS patients; 18% of patients with CCHS and HSCR). A long colonic segment was affected in both patients, a mediastinal ganglioneuroblastoma was detected in an 8-year-old girl, and an abdominal neuroblastoma was detected in a 5-month-old boy.

In addition, one male patient (< 1% of CCHS patients) had CCHS and growth hormone deficiency. The latter was diagnosed as the child presented with recurrent hypoglycemic episodes at 6 months of age.

The most important moments of the disease course were as follows:

1. The first symptoms were present at birth or in the first days of life in all patients. In one case, fetal cardiac arrhythmia (*ie*, chaotic atrial tachycardia and flutter) was detected in the last month of pregnancy and was treated by antiarrhythmic drugs that were administered to the mother.
2. The median age at diagnosis was 3.5 months (range, 0.5 to 15 months) before 1995 and decreased in the last 5 years. All recent cases were recognized in < 2 weeks after the onset of respiratory symptoms ($p = 0.01$). The median age at tracheostomy was 3 months (range, 1.5 to 6 months).
3. The median age at first hospital discharge was 9 months (range, 3 months to 11 years). The presence of associated HSCR significantly delayed the first hospital discharge (isolated CCHS, 9 months [range, 3 to 70 months]; CCHS and HSCR, 12 months [range, 6 to 132 months]; $p = 0.02$). Three patients born in the early 1980s spent 3, 8, and 11 years in various ICUs or in long-term care centers before being discharged to their homes. In the last decade, the home setting is our first option at the initial hospital discharge. However, the median age at first hospital discharge did not differ before and after 1995 ($p = 0.18$). In contrast, the longest duration of hospitalization was dramatically reduced in the recent years (16 months after 1995, instead of 11 years before 1995).

Clinical Outcome

Figure 1 displays the Kaplan-Meier plot showing the survival rate starting from birth for the whole group. The median survival age was 20 years. The 43 CCHS patients who were alive consisted of 11 male patients and 32 female patients (sex ratio, 0.4). Their age at the time was 9 years (range, 2 months to 27 years). All patients lived full-time at home, except for one patient who resided in a long-term care center and two young infants who were still in the hospital having recently received a diagnosis. Two patients had been adopted at a young age. Seven patients (16%) were young adults who were > 20 years old. Four of them lived alone. The highest educational level obtained was a university master's degree. One patient had a full-time occupation, two patients had various fixed-term contracts, and three patients were following training programs. None of them was married or had children.

The overall mortality rate was 38% (95% CI, 27 to 49%). Twenty-seven patients died (18 male patients and 9 female patients; sex ratio, 2). Little information was available for 11 of the 15 patients who died before 1995. The median age at death was 3 months (range, 0.4 months to 21 years). A total of 22 patients (81%) died before the age of 2 years, 3 died during early childhood, 1 died during adolescence, and 1 died as a young adult. The 2-year mortality rate was significantly greater for male patients than for female patients ($p = 0.02$; RR, 2.71; 95% CI, 1.14 to 6.47) [Fig 2]. In contrast, it was affected neither by the presence of associated HSCR ($p = 0.93$; RR, 0.95;

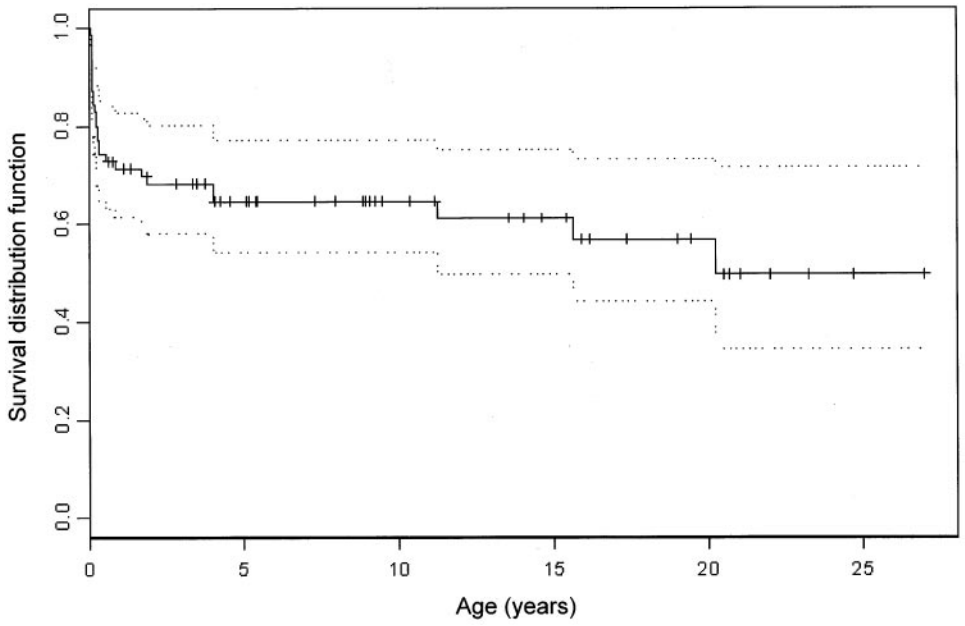

FIGURE 1. Kaplan-Meier plot showing survival data starting from birth for the whole group. Solid line = estimated survival curve; broken line = the 95% CI; + = actual ages of patients.

95% CI, 0.28 to 3.2) nor by different values before and after 1995 (p = 0.7; RR, 0.85; 95% CI, 0.37 to 1.97).

Death occurred at the hospital in young infants and was related to ethical decisions (five patients), severe dysautonomia (two patients), cor pulmonale (one patient), viral infections (two patients), recurrent episodes of sudden bronchial obstruction in a tracheotomized patient resulting in totally ineffective mechanical ventilation (one patient), or unsuccessful treatment of neuroblastoma (one patient). Six deaths occurred at home, following severe pulmonary infections (three patients) or an accidental decannulation (in the early 1980s). In addition, one adolescent who became nonobservant to nighttime noninvasive ventilation and one

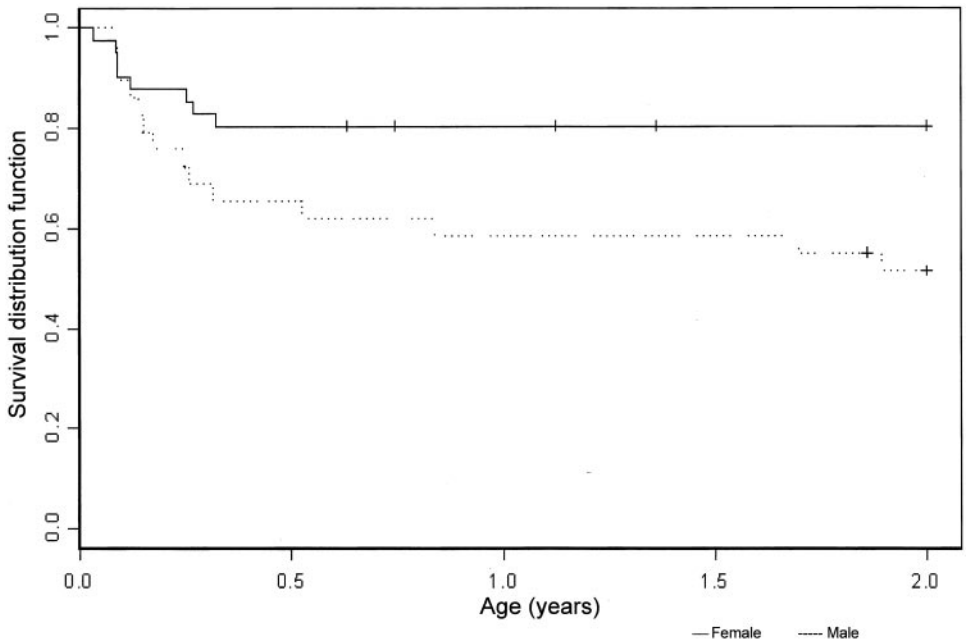

FIGURE 2. Comparison of survival data before age of 2 years between female patients with CCHS (solid line) and male patients with CCHS (broken line) [p = 0.02; RR, 2.71; 95% CI, 1.14 to 6.47].

young adult who was receiving phrenic nerve stimulation during sleep were found dead in bed.

Respiratory Status

All patients required ventilatory support during the neonatal period. Among the 50 patients who lived beyond 1 year of age, all but 1 received nighttime ventilatory support (Fig 3). A 4-year-old girl did not receive mechanical ventilation during sleep. She presented at 3 months of age with a typical pattern of CCHS with alveolar hypoventilation that was most severe during slow-wave sleep, reduced hypercapnic ventilatory responses, diminished heart rate variability, and mild ocular dysmotility. Sleep hypoventilation was significantly less severe after treatment with caffeine (overnight end-tidal P_{CO_2}, 52 to 56 mm Hg; minimal oxygen saturation, 90 to 92%). Follow-up included at least a clinical evaluation and full overnight sleep studies every 4 months, and echocardiography every 6 months (unpublished case). In addition, three patients (6%) also required daytime ventilatory support because of severe hypoventilation during spontaneous breathing. All three patients had CCHS and HSCR (short-segment HSCR, two patients; total colonic HSCR, one patient). One patient received assisted ventilation 24 h/d, and two patients received bilateral phrenic nerve stimulation.

Intermittent positive-pressure ventilation was delivered during sleep using tracheostomy in 39 patients (78%) and using a mask in the other 10 patients (20%) [nasal mask, 9 patients; nasobuccal mask, 1 patient]. One child had never undergone tracheostomy. The transition to nasal ventilation was performed at 8 years of age for the youngest patient. Turbinectomy was required to relieve upper airway obstruction in two patients (before transfer to nasal ventilation, one patient; after transfer to nasal ventilation, one patient).

Genotype

Thus far, 34 patients have been tested. Heterozygous *PHOX2B* mutations were identified in 31 patients (91%), most of them consisting of alanine expansions within the polyalanine tract. The *PHOX2B* mutation was associated with other mutations in five patients (mutation of the glial cell-derived neurotrophic factor gene, two patients [*de novo* in one patient and inherited from a healthy mother in the other patient]; mutation of the *receptor tyrosine kinase* gene inherited from a healthy father, one patient; and mutation of the *HASH-1* gene, two patients [*de novo* in one patient and inherited from a healthy father in the other patient]). Finally, an additional patient had a mutation of the *HASH-1* gene only (parent's blood not available for

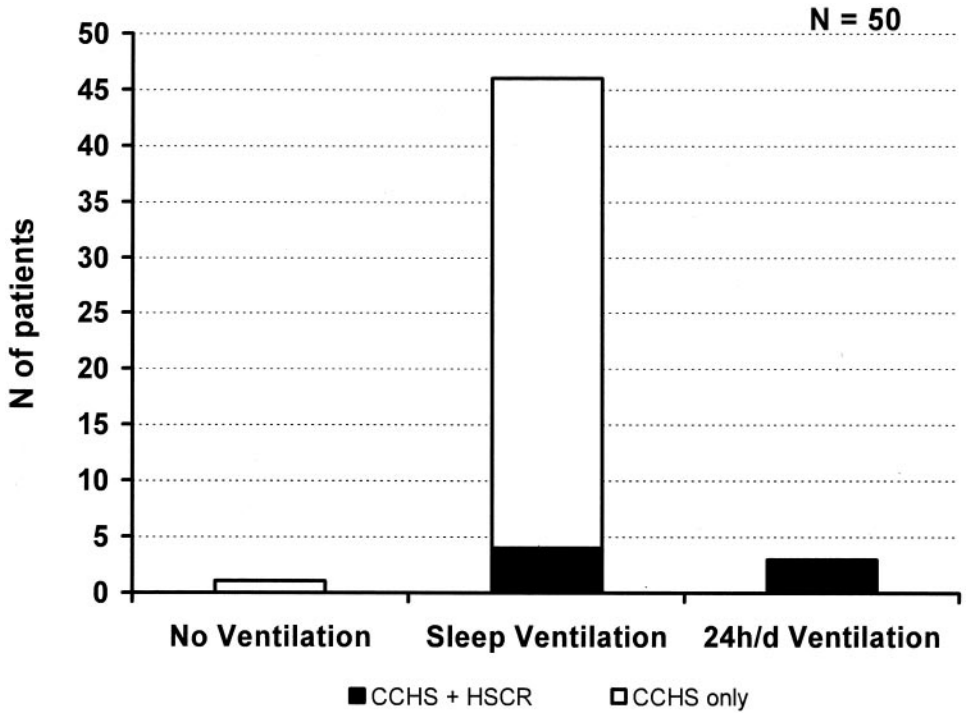

FIGURE 3. Respiratory status of the 50 patients who lived beyond 1 year of age, as a function of associated HSCR.

testing) without an identifiable *PHOX2B* gene mutation. None of the patients tested had a mutation in genes encoding respiratory neuron homeobox,[9] neurturin, endothelin-3, endothelin-B receptor, or brain-derived neurotrophic factor.

Discussion

This study provides data from a unique, country-wide cohort of patients with CCHS. This is the first description of the French CCHS population as a whole.

Incidence

This study is also the first to allow an estimation of the incidence of CCHS. In the last 5 years, we recorded an average of four new cases per year. As the number of live births is approximately 780,000 per year in France, the incidence of CCHS may be estimated at approximately 1 per 200,000 live births in our country. Thus, CCHS may be regarded, not as a rare disease (*ie*, defined by an incidence of < 1 per 2,000 live births), but as an extremely rare disease. The number of new patients in the last few years was nearly twice as high as that in the early 1980s. Although an increase in CCHS cannot be excluded, we think, however, that the most likely reason is greater identification of the disease. Integrated efforts have been made to create a French CCHS working group and a CCHS center, as well as an organization of French CCHS families. By means of medical conferences, review articles, and networking, much has been done to emphasize the existence and prognosis of the disease among French neonatal and pediatric caregivers. Moreover, these actions likely account for the shorter delay in diagnosis observed in the last few years.

Phenotype

Sixteen percent of our CCHS patients also had HSCR. The varying percentages of the CCHS and HSCR phenotype across previous studies (up to 50%) were likely due to skewed patient recruitment.[5–8] Some studies were based on a retrospective review of published case reports, and the others involved patients with DNA testing only. Conversely, a recent international survey[10] using questionnaires sent to 196 families of CCHS patients (among which 17 were French) found a proportion of HSCR similar to that of our cohort. HSCR is a condition caused by the congenital absence of parasympathetic intrinsic ganglion cells in submucosal and myenteric plexuses that is thought to be related to a failure of the migration of neural crest-derived cells.[11] A large series[11] previously reported that 80% of the patients with isolated HSCR were men, and that a short colonic segment was involved in 80% of the cases. The distribution of HSCR variants in our CCHS patients differed greatly from that reported in isolated HSCR. We found a similar prevalence of CCHS and HSCR in male and female patients, and in 80% of the cases a long colonic segment was affected. The mortality rate of the CCHS and HSCR phenotype found in our cohort (45%) was much higher than the 6% previously reported for patients with isolated HSCR.[12] However, the mortality rate did not differ from that of patients with isolated CCHS in the current study. In most cases, the presence of HSCR significantly increased the length of hospitalization and the morbidity of CCHS patients. It is noteworthy that all our three patients who required ventilatory support 24 h per day had associated HSCR.

Our cohort included one male CCHS patient with a growth hormone deficiency. As far as we know, another case with a similar phenotype has been reported in a female patient.[13] Both patients shared some similarity with a subset of patients with late-onset central hypoventilation syndrome and endocrine disorders suggestive of hypothalamic dysfunction.[14] However, whether these two syndromes have the same physiopathologic bases remains unclear.[15] Thus, it may be of interest to perform systematic endocrine investigations in CCHS patients to increase our understanding of this phenotype, which also involves the hypothalamic-pituitary axis.

Finally, CCHS was observed in one pair of twins and one pair of siblings in our cohort. The first familial cases of CCHS were reported in the late 1980s[16,17] and strongly supported a genetic origin of the condition, long before the recent identification of the *PHOX2B* gene mutation.[8]

Genotype

A high frequency of mutations in genes implicated in autonomous differentiation was found in our patients. The discovery of *PHOX2B* gene mutations in patients with CCHS constituted the most important contribution to the understanding of the genetics of this condition[8] and was confirmed by other studies.[18,19] *PHOX2B* is a transcription factor belonging to signaling pathways that are known to be essential for early autonomic nervous system development.[20,21] These findings are consistent with an autosomal-dominant pattern of inheritance for CCHS and, in accordance with parent-infant transmission of CCHS,[17] a high prevalence of associated HSCR and varying degrees of autonomic nervous dysfunction observed in the patients.[22] A further

understanding of the mechanisms of *PHOX2B* gene mutation is required before recommendations can be provided for genetic counseling and pregnancy planning for families of CCHS patients.

Outcome

The overall mortality rate was as high as 38% (95% CI, 27 to 49%) in our cohort. Rates of 8%[5] and 31%[6] have been reported in two previous studies. However, these included one with center-derived data and a smaller number of patients, and therefore precludes comparisons between these data and ours. Surprisingly, the mortality rate was unaffected by an association with HSCR in our study. More interestingly, we found a higher mortality rate in male patients than in female patients. As testosterone has been shown to depress the central ventilatory drive in the sleeping infant primate, one may speculate on the presence of more severe disease in male patients.[23] Nevertheless, causes of death of patients with CCHS are multiple in many cases and appear to be directly linked with high morbidity that is related to tracheostomy and ventilator dependence. In the meantime, death in older patients is thought by the medical community to be a failure in care. Lifelong dependence on ventilatory support is a real challenge for the patients. One adolescent became noncompliant to nighttime nasal mask ventilation despite repeated explanations and admonitions, and died during sleep. The option of "decannulation/nasal ventilation" is a relatively recent demand of young CCHS patients. Nasal mask ventilation has been successfully used to treat central hypoventilation in many CCHS patients in France and abroad.[2,3,24] Furthermore, it may prevent tracheostomy-related lung infections, and daily care of the tracheostomy is no longer required. We have no experience in the other ventilatory support options (such as negative-pressure ventilation) that have been reported elsewhere.[25]

Health-Care Organization

A recent survey[10] among families of patients with CCHS showed the extent of the health-care burden produced by this challenging condition. Multidisciplinary follow-up and technology-dependent care are required during the patient's lifetime. Health-care organizations are largely dependent on the health policy in each country. In France, the medical costs for CCHS patients are fully covered by public funds. Additional public financial aid is available to allow one parent either to have a part-time professional occupation or to stay at home to care for the child.

In the last decade, we have organized health care for CCHS patients as a four-level structure, as follows: (1) the base consists of parents and families from whom major efforts are required for the daily care of the child; (2) the second level, which includes at least a family practitioner, a respiratory physiotherapist, and technical assistants, aims to provide first care at the patient's home; (3) the third level is the local hospital, which in most cases had provided the initial care to the child at birth, and some local hospitals are equipped with many medical specialties; and, finally, (4) the fourth level is the national CCHS center, which allows the diagnosis, multidisciplinary follow-up, and treatment of patients, and coordinates management of the disease across physicians and service providers. In addition, the CCHS center gathers patient data and provides recommendations about patient monitoring and management, and expertise on new ventilators or particular treatments (*eg*, the transition to nasal ventilation or phrenic nerve stimulation).

CCHS has long been thought of as a childhood disease, but the life expectancy for patients with CCHS now reaches well into adulthood. Our cohort included seven young adults who were alive and were >20 years of age. Patients growing up with CCHS experience many challenges. Thus far, no research had examined the psychosocial impact of CCHS on becoming an adolescent and an adult, the achievement of independence, as well as concerns about life, health, and finances. One of the missions of our CCHS center is to develop and coordinate the transition process from pediatric to adult care settings.

In summary, the four major findings of this study are the extreme rarity of CCHS (incidence estimate, 1 per 200,000 live births in France), the improved recognition of the disease due to an integrated multicenter effort, the lack of effect of HSCR on mortality, and the high frequency of *PHOX2B* gene mutations. This study provides an overview of the French CCHS population. The French CCHS Registry is an ongoing, prospective, and observational database. As CCHS is an extremely rare disease, collaborative efforts should be made to establish the International CCHS Registry. Increased knowledge about the disease gives rise to a great hope for the improved diagnosis of the disease and improved management of these patients.

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Appendix: The French CCHS Working Group

Groupe Francophone de Réanimation et Urgences Pédiatriques: J. Camboulives (Marseille); B. Delaporte (Le Havre); J.L. Demarquez (Bordeaux); D. Devictor (Paris); L. Egreteau (Reims); G. Ensel

(Rouen); D. Floret (Lyon); P. Hubert (Paris); F. Leclerc (Lille); J. Messer (Strasbourg); M. Moktari (Paris); G. Moriette (Paris); D. Oriot (Poitiers); J.C. Rozé (Nancy); D. Rieu (Montpellier). All are physicians from neonatal and pediatric ICUs.

INSERM U-393, Département de Génétique, Hôpital Necker Enfants Malades: S. Lyonnet (Paris).

Unité d'Epidémiologie Clinique, Hôpital Robert Debré: C. Alberti (Paris).

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Ha Trang, Michel Dehan, François Beaufils, Isabelle Zaccaria, Jeanne Amiel and Claude Gaultier

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