Pediatric Pulmonology 37:217–229 (2004)

Epidemiologic Survey of 196 Patients With Congenital Central Hypoventilation Syndrome

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Summary. This study examined the cross-sectional medical and social characteristics of children diagnosed with congenital central hypoventilation syndrome (CCHS). A detailed questionnaire was mailed to all families with a child with CCHS who are affiliated with a family network or support group. The questionnaire response rate was >75% (n = 196). Mean age was 10.22 years ±6.6 years (SD) (range, 0.4–38 years), with a 1:1 sex ratio. Multisystem involvement was almost universal among the cohort, with Hirschsprung's disease (HD) present in 16.3%; 61.7% of the children had a tracheotomy, but 14.3% were never tracheotomized, with 77 subjects (39.3%) not having a tracheostomy tube at time of survey. Respiratory support approaches varied but clearly reflected the trend towards earlier and more widespread transition to noninvasive ventilatory modalities. Significant developmental problems were noted, but attendance in regular classes occurred in the majority. Significant deficiencies in routine periodic evaluation and management were reported. In addition, the presence of CCHS was associated with a significant financial and psychosocial burden to the families. In conclusion, a comprehensive survey of 196 CCHS children and their families revealed a cross-sectional picture of substantial medical and psychosocial complexities associated with this disorder, and pointed out substantial inadequacies in routine preventive care that appear to impose stress on the families. The emerging trend of earlier transition to noninvasive ventilatory support warrants future studies. Implementation of recommended guidelines for diagnosis and multidisciplinary follow-up of CCHS should ultimately ameliorate the long-term outcome of this lifelong condition. **Pediatr Pulmonol. 2004; 37:217–229.** © 2004 Wiley-Liss, Inc.

Key words: CCHS; tracheostomy; noninvasive mechanical ventilation; psychomotor development; diaphragmatic pacemakers.

INTRODUCTION

Congenital central hypoventilation syndrome (CCHS), initially reported by Mellins et al. in 1970,[1] is a relatively rare lifelong multisystem disorder characterized by autonomic nervous system dysfunction, which most dramatically manifests as failure to maintain ventilatory homeostasis during sleep. The estimated incidence of CCHS is approximately 1 in 50,000 live births,[2] and recent evidence suggests that the clinical manifestations of CCHS correspond to the spectrum of clinical problems attributable to neural crest dysfunction.[3] Indeed, CCHS has been associated with Hirschsprung's disease (HD),[4,5] loss of respiratory modulation of heart rate as well as occurrence of cardiac arrhythmias,[6] reduced or absent central chemosensitivity and dyspnea,[7,8] and multiple ocular problems.[9] While there is increasing evidence of a genetic link in CCHS,[10] the disease etiology and pathophysiology still remain under investigation, since no specific gene or lesion can account for the clinical phenotypic spectrum. Notwithstanding such limitations, technological advances and expansion of mechanical ventilatory support options have been associated with improved prognosis for CCHS patients, further justifying efforts to increase awareness among medical professionals of this condition.[11]

Increased networking among families and physicians of CCHS patients, and several reports in the medical

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Grant sponsor: NIH; Grant number: HL-65270; Grant sponsor: Department of Education; Grant number: H324E011001; Grant sponsor: Commonwealth of Kentucky Research Challenge Trust Fund.

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Received 3 March 2003; Revised 1 September 2003; Accepted 8 September 2003.

DOI 10.1002/ppul.10438
Published online in Wiley InterScience (www.interscience.wiley.com).

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literature on small populations of CCHS patients and their unique medical characteristics, have allowed for some familiarization with this disorder.[12,13] However, because of the rarity of CCHS, many primary-care physicians are unaware of the diagnosis, or may treat only one of these special patients during their professional careers.

Therefore, we conducted a large-scale survey of CCHS children and young adults, to assess the range of medical and homecare issues affecting CCHS children and their families, and to gain some insights into potential problems facing these families during their daily lives in the community.

METHODS

Questionnaires in five languages were mailed to the families of CCHS patients from around the world who are registered with the CCHS Family Network in the US and Europe. Language translation assistance was provided by medical doctors who were also parents of CCHS children (for the German and Italian survey instruments) or by well-informed, bilingual CCHS parents (Spanish and French versions). Completed questionnaires were returned from 19 countries by 196 CCHS families or patients between October 2001–February 2002, corresponding to a response rate of over 75%. The great majority of respondents were from socioeconomically more affluent, postindustrial countries, including the US (90), Germany (24), France (17), Italy (17), UK (12), Canada (6), Spain (6), Australia (3), Denmark (3), and Switzerland (3). CCHS families from nine other (non-Western) countries also returned completed surveys. Respondents could choose to remain anonymous, if they so desired.

Family caregivers were queried on a range of issues pertaining to the CCHS patient's medical condition and health management, types of ventilation in use and other medical equipment in the home, physician visits and hospitalization, annual medical evaluations, learning and school issues, medical and financial support for home care, and family lifestyle. Survey items were designed to yield insight into issues raised by CCHS families and their physicians over the years. Formal family networking, particularly in North America and France, has raised awareness of the challenges faced by these technology-dependent children and their families, and has prompted renewed efforts and interest in optimizing the management of these medically complex children at home. A 1996 study by one of the authors on the demographics of CCHS populations in North America (94 subjects) identified additional patterns of medical issues faced by that subset of CCHS patients.[14] Survey questions were informed by these strands of information, as well as by case reports and other published research detailing medical characteristics of smaller CCHS populations. Descriptive statistics were employed to tabulate and assess data. Means and standard deviations were calculated. Standard *t*-tests and one-way analysis of variance were used as appropriate.

RESULTS

Population Demographics

The diagnosis of CCHS was established by polysomnography and after an appropriate clinical evaluation by pediatric specialists with expertise in this condition in all 196 children included in this report. Of note, polysomnography was conducted in all children, and hypercapnic challenges were performed at least once in 184 children (data missing for the remaining 12 children). The mean population age was 10.22 ± 6.6 years (range, 0.4–38 years), with a 1:1 sex ratio. Thirteen of the 196 subjects were over 20 years old, while 59 were age $\leq$5 years. Forty-two (21.4%) of the children were born prematurely, with a mean gestational age of 31.8 ± 7.6 weeks for that group. Height and weight averaged in the 45th percentile, with only 7 children at less than 5% for height and weight. Most subjects (93.9%) lived at home full time: 90.8% of them with their biological parents, and the others with close relatives. Three percent of subjects were adopted. Four children (2.5%) lived in a long-term care facility. The population included two sets of identical twins (both twins affected), and one pair of siblings with CCHS.

Twenty (10.2%) CCHS subjects were identified by caregivers as 24-hr ventilator-dependent. Another 81.6% (160) were identified as requiring mechanical ventilatory support only while asleep, while 4.1% (8) additional children received mechanical ventilation during sleep plus another hour sometime during the day. Finally, 3.6% (7) were mechanically ventilated during sleep as well as during several hours during daytime.

Nearly two-thirds (61.7%) of the subjects had a tracheotomy, but 14.3% (28) of the children had never been tracheotomized, with 77 subjects (39.3%) not having a tracheotomy tube at time of survey. A country breakdown of frequency of tracheotomy among CCHS patients highlighted differences in medical practice and ventilation methods between the US and Europe. Whereas 24.4% (22 of 90) US CCHS patients were managed without a tracheotomy, 53.4% (47 of 82) of the CCHS subjects in Europe were ventilated without tracheotomy (χ^2, Mantel-Haenszel corrected, $P < 0.0001$). In addition, wide differences were apparent in the percentage of children treated without tracheotomy among the larger European countries: France, 35.3%; UK and Germany, 66.7%; and Italy, 47.1%. These findings may further reflect the fact that transition to noninvasive ventilation (i.e., ventilatory support without tracheotomy) has become routine for patients who are ventilator-dependent only during sleep, albeit at different rates across countries. Figure 1 depicts the age pattern of decannulation in these CCHS subjects.

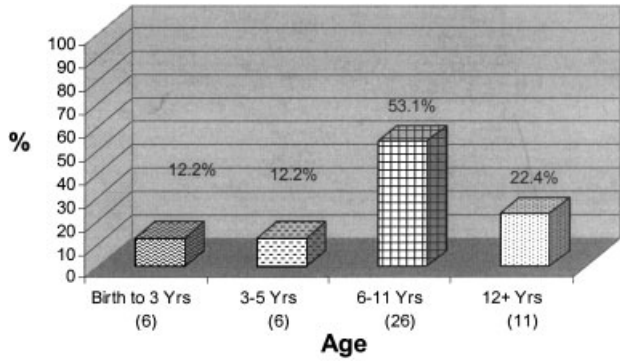

Fig. 1. Age at decannulation (n = 49): percent of those tracheotomized. An additional 14.3% (28) of children were never tracheotomized.

Medical Issues Associated With CCHS

Table 1 reports the frequency of various medical diagnoses potentially associated with CCHS, and compares total population figures with subsets of patients requiring mechanical ventilatory support either only during sleep or for 24 hr. Of note, 15 children reported as receiving some minor ventilatory support during daytime were included in the sleep-only ventilated group.

Hirschsprung's disease

Hirschsprung's disease (HD) was present in 16.3% of all CCHS children, and was more likely in children receiving mechanical ventilation for 24 hr a day (25%; n = 5). Only two respondents (1.0%) reported a family history of HD. The initial surgical treatment for HD consisted of a colostomy/ileostomy in 90.0% (27/30), and of one-stage pullthrough surgery in the remainder. Postsurgical complications reported for the 32 CCHS-HD diagnosed children included: encopresis (28.1%, 9); constipation (25.0%, 8); necrosis of the bowel wall (6.3%, 2); failure to gain weight (40.6%, 13); and bloody stools (15.6%, 5).

Other medical conditions

Other conditions affecting at least 15% of all CCHS subjects included: gastroesophageal reflux, need for gastrostomy tube feedings during infancy, constipation, diarrhea, premature birth, fainting episodes, seizures (primarily during infancy), cardiac arrhythmias, cor pulmonale, complaints of leg pain and of excessive yawning during exercise, episodes of profuse sweating and cool extremities, absence of fever with infections, asthma, recurrent pneumonia, hypotonia, and ophthalmologic and dental issues. Notably, developmental and motor and speech delays and learning disabilities were reported in >25% of the CCHS population surveyed. In addition, >50% of CCHS children received or are currently receiving both physical therapy (54.6%, 107) and speech therapy (65.8%, 129). Other less frequent medical issues further provide a clinical picture of multiple organ involvement, and emphasize that CCHS represents a complex medical condition that is associated with a considerable health burden.

Hospital Discharge After Birth

By age 7 months, only 44.6% of the sleep-only mechanically ventilated CCHS children (n = 176) and 35.4% of the CCHS children with HD (n = 32) were discharged to their homes (Table 2). For the 24-hr ventilator-dependent CCHS children (n = 20), 65.0% were discharged by age 7 months.

Ventilation Methods

Data on the ventilatory-support approaches used in CCHS children are summarized in Figure 2. Of those patients receiving mechanical ventilation via tracheotomy, 97 (49.5%) used a pressure or volume home ventilator, and 4 (2.0%) used a bilevel positive-pressure device. An additional 28.1% (55) of CCHS patients used nasal or facemask ventilation without a tracheotomy, with half of these using their home ventilator, and the other half using a bilevel positive-pressure device. Five CCHS children (2.6%) used negative-pressure ventilators without tracheotomy. Of those patients receiving noninvasive ventilation, 71.4% used mask ventilation, 6.5% used negative pressure, and 22.1% used diaphragmatic pacers.

Of the 40 CCHS patients using diaphragmatic pacing, 40% used their pacers only at night (typically without a tracheotomy) and as their sole source of ventilation support. Seventeen children (42.5%) used diaphragmatic pacers during the day, and received mechanical ventilation via tracheotomy at night. Two subjects (5.0%) used diaphragmatic pacers during daytime and mask ventilation (no tracheotomy) at night. Figure 3 summarizes the age profile of those using noninvasive ventilation.

Half of the children (95) changed ventilatory support methods over time, with parents citing ''increasing portability'' and ''getting rid of the tracheostomy'' as their principal motivations. In 46.4% of these cases, the child or family suggested or initiated the change in ventilatory support method, while physicians or other medical professionals suggested such a change in 35.1%. Typically, the transition to noninvasive ventilation occurred between the ages 6–11 years. However, 20 of 59 children (33.9%) aged 5 years or younger were using noninvasive ventilation.

Awake Hours Off the Ventilator

While most CCHS children breathe adequately while awake and do not require 24-hr ventilatory support, this

TABLE 1— Medical History of 196 CCHS Children[1]

	Gender M:F	% pop	All		Sleep only n = (176)		24-hr n = (20)	
	51/48	89.8						
Sleep only 24-hr	40/60	10.2	(n)	%	(n)	%	(n)	%
Hirschsprungs disease			(32)	16.3	(27)	15.7	(5)	25
Other gastrointestinal motility disorder			(23)	11.7	(18)	10.2	(5)	25
Gastroesophageal reflux			(35)	17.9	(28)	15.9	(7)	35
Tracheomalacia			(26)	13.3	(21)	11.9	(5)	25
G-tube feedings			(50)	25.5	(45)	25.6	(5)	25
Absent gag reflex			(21)	10.7	(19)	10.8	(2)	10
Premature birth			(42)	21.4	(35)	19.9	(7)	35
Recurrent fainting episodes			(49)	25.0	(41)	23.3	(8)	40
Seizures			(82)	41.8	(68)	38.6	(14)	70
Currently on anti-seizure medications			(25)	12.8	(16)	9.1	(9)	45
Cardiac arrhythmias			(37)	18.9	(30)	17.0	(7)	35
Cardiac pacer			(8)	4.1	(7)	4.0	(1)	5
Cor pulmonale			(33)	16.8	(29)	16.5	(4)	20
Blurred vision with standing			(27)	13.8	(24)	13.6	(3)	15
Complaints of leg pains			(59)	30.1	(22)	12.5	(4)	20
Yawns during exercise			(40)	20.4	(32)	18.2	(8)	40
Sweating, cool extremities			(84)	43.0	(71)	40.3	(13)	65
No fever with infections			(44)	22.4	(38)	21.6	(6)	30
Recurrent pneumonia			(81)	41.3	(69)	39.2	(12)	60
Recurrent constipation			(45)	23.0	(41)	23.3	(4)	20
Recurrent diarrhea			(38)	19.4	(29)	16.5	(9)	45
Asthma			(34)	17.3	(31)	17.6	(3)	15
Hypotonia			(54)	27.6	(43)	24.4	(11)	55
Motor delays			(89)	45.4	(76)	43.2	(13)	65
Absent or abnormal tears			(57)	29.1	(51)	29.0	(6)	30
Ophthalmological problems			(91)	46.4	(81)	46.0	(10)	50
Wears corrective lenses			(73)	37.2	(67)	38.1	(6)	30
Depth perception impaired			(29)	14.8	(24)	13.6	(5)	25
Unequal pupil size			(37)	18.9	(34)	19.3	(3)	15
Strabismus			(59)	30.1	(50)	28.4	(9)	45
Abnormal pupil dilation			(37)	18.9	(32)	18.2	(5)	25
Hearing loss			(19)	9.7	(18)	10.2	(1)	5
Chronic ear infections			(55)	28.1	(48)	27.3	(7)	35
Dental/orthodontic issues			(88)	44.9	(81)	46.0	(7)	35
High number dental caries			(44)	22.4	(39)	22.2	(5)	25
Late retention baby teeth			(25)	12.8	(21)	11.9	(4)	20
Underbite/protrudent jaw			(39)	19.9	(36)	20.5	(3)	15
Precocious puberty			(12)	6.0	(10)	5.7	(2)	10
Obesity			(6)	3.1	(5)	2.8	(1)	5
Growth hormone deficiency			(4)	2.0	(4)	2.3	(0)	0
Hypoglycemia			(17)	8.7	(13)	7.4	(4)	20
Hypothyroidism			(5)	2.6	(4)	2.3	(1)	5
Neural crest tumor (benign)			(7)	3.6	(6)	3.4	(1)	5
Neural crest tumor (malignant)			(2)	1.0	(2)	1.1	(0)	0
Crohn's disease			(3)	1.7	(3)	1.7	(0)	0
Enterocolitis			(4)	2.0	(3)	1.7	(1)	5
Rheumatoid arthritis			(2)	1.0	(2)	1.1	(0)	0
Autism or pervasive developmental disorder			(3)	1.7	(2)	1.1	(1)	5
Birth defects			(15)	7.7	(13)	7.4	(2)	10
Family history of birth defects			(5)	1.7	(5)	2.8	(0)	0
Nocturnal enuresis			(3)	1.5	(2)	1.7	(1)	5
Unusual bleeding with Injury			(15)	7.7	(12)	6.8	(3)	15
Neurodevelopmental issues								
Developmental delays			(88)	44.9	(75)	42.6	(13)	65.0
Formal diagnosis of learning disabilities			(58)	29.6	(50)	28.4	(8)	40.0
ADD/ADHD			(25)	12.8	(23)	13.1	(2)	10.0
Anxiety disorder			(15)	7.7	(12)	6.8	(3)	15.0
Depression			(8)	4.1	(7)	4.0	(1)	5.0
Obsessive/compulsive disorder			(14)	7.1	(10)	5.7	(4)	20.0

(*Continued*)

TABLE 1—(*Continued*)

Speech delays	(100)	51.0	(85)	48.3	(15)	75.0
Motor delays	(89)	45.4	(76)	43.2	(13)	65.0
Received speech therapy	(129)	65.8	(113)	64.2	(16)	80.0
Received physical therapy	(107)	54.6	(93)	52.8	(14)	70.0

[1]Sleep only, require mechanical ventilation only during sleep; 24-hr, require mechanical ventilation all day.

ability is typically not present in the first months of life (Fig. 4). Among those CCHS children requiring mechanical ventilation during sleep only, 34.1% (60) could spend most awake hours off the ventilator from birth, 19.9% (35) were 6 months old, and an additional 11.9% (21) were 7–12 months old before they could spend significant awake time without ventilatory support. Of the remaining 46 children, one half (13.1%, 23) were 12–18 months of age, and the other half (13.1%, 23) were older than 18 months of age before they could spend most of their awake hours off the ventilator. In other words, two-thirds of these children were able to adequately maintain ventilatory homeostasis during waking hours by age 12 months, while another quarter of the children were 1or more years older before they achieved such an ability.

Conscious Breathing

CCHS families were also queried as to whether they and the child's other caregivers regularly cued their children to take breaths (or, for older patients, whether they consciously cued themselves to take more breaths). Of those children who were old enough to understand and follow instructions, 60.6% (83) were cued by themselves or others to take additional breaths, especially during exercise. Figure 5 depicts the frequency of conscious breath-taking maneuvers across various age groups. Thus, for many older CCHS subjects and their care providers, constant vigilance and awareness of breathing is present even during periods of waking.

Medical Evaluations and Physician Contacts in CCHS

The frequency of medical tests among this population of technology-dependent patients is summarized in Table 3. Across the full range of tests typically recommended for CCHS patients,[15] a higher frequency of annual evaluations emerged among the 24-hr ventilated CCHS population compared to the sleep-only ventilated children. However, a substantial proportion of CCHS patients did not receive periodic cardiorespiratory monitoring in the laboratory. Even among the more severely affected subjects, such as those who needed ventilatory support full time, only 50% underwent polysomnography, ECG, and neurological assessments annually. In fact, 55% of 24-hr ventilator-dependent children reported that a 24-hr Holter test was never performed, and approximately 30% reported never undergoing a pulmonary function test, neurological assessment, or bronchoscopic evaluation. Among all CCHS responders, the large majority did not have annual monitoring in a hospital or clinical setting. The exception is that 55% of CCHS patients received an eye/vision evaluation annually.

In an effort to assess indicators of health requirements of the CCHS population, the survey inquired about the frequency of physician contacts and hospital admissions. In general, the number of physician visits and hospital admissions were highest in the first few years of life and decreased for most CCHS patients thereafter. Nevertheless, the health burden in care for these children remained substantial. Indeed, for the total population of CCHS, the mean number of hospitalizations in the preceding 12 months was 0.96 ± 1.4 (range, 0–11), and the mean number of doctor visits in that period was 7.85 ± 8.40 (range, 0–52).

Overall, 48.9% (88) of CCHS children for whom information was available (n = 180) had no hospital admissions in the previous year, and 28.3% (51) required only one hospitalization during that period. However, only 33.3% (18) of children ≤5 years old, 47.5% (19) of 6–10-

TABLE 2—Age at Hospital Discharge After CCHS Diagnosis[1]

							CCHS-HD	
	Total %	187 (n)	SO (%)	168 (n)	24-hr (%)	20 (n)	(%)	31 (n)
Up to 3 months	20.9	41	20.2	34	35.0	7	19.4	6
3–6 months	24.0	47	24.4	41	30.0	6	16.1	5
7–12 months	24.5	48	27.3	46	1.0	2	29.0	9
>12 months	26.0	51	28.0	47	25.0	5	35.5	11
Missing data: n		9		8				1

[1]SO, sleep only, mechanical ventilation only during sleep; 24-hr, mechanical ventilation all day; CCHS-HD, CCHS with Hirschsprung's disease.

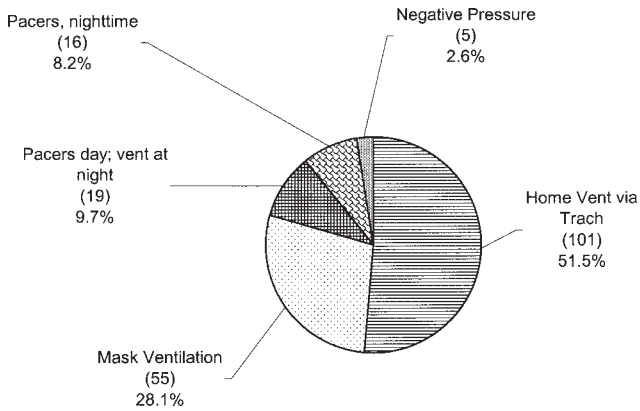

Fig. 2. Ventilation modalities in CCHS, 2002 (n = 196).

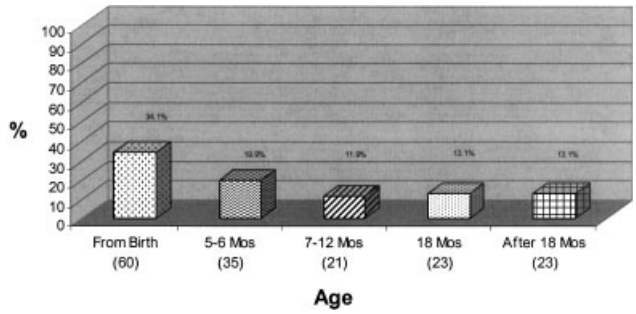

Fig. 4. Age at which sleep-only ventilated spent most awake hours off ventilator (n = 162, 14 missing or could not recall; 20 others, 24-hr ventilated).

year-olds , 59.6% (28) of 11–15-year-olds, and 69.6% of 16–20-year-olds had no hospitalizations in the preceding year.

Table 4 summarizes these data and also compares children requiring mechanical ventilation during sleep or throughout the day. Figure 6 depicts hospital admissions data for 160 CCHS patients who received mechanical ventilation for sleep only. A greater healthcare burden was present among the 24-hr ventilator-dependent patients; however, the need for hospitalization decreased with age in both groups.

Data on physician contacts in the previous 12 months (n = 174) again reflect a reduced need for intervention by medical professionals as the CCHS child ages. Table 5 displays data for the entire CCHS population, as well as for children requiring mechanical ventilation during sleep or for 24 hr. Figure 7 highlights the data for 154 CCHS patients who required ventilatory support only during sleep. Overall, 55.7% (98) of patients had 5 or more physician contacts, 36.9% (65) had 7 or more doctor visits in the previous year, and 27.8% (49) had 10 or more doctor visits in the preceding 12 months. As with hospital admissions, these data reflect both the frequent and periodic monitoring and medical intervention required by the youngest children with CCHS, and the regular professional monitoring needed by all CCHS patients in order to optimize their health status.

General pediatricians monitored the routine care of approximately half (49.9%, 98) of the CCHS patients in this study, 30% (56) of the patients saw a pediatric pulmonologist for routine care, and 7.7% (14) saw a CCHS specialist at a research facility for their routine medical care. Nearly a quarter of the CCHS population (24.5%, 48) reported that they never saw a CCHS specialist, while another 14.3% (28) reported that they saw a specialist irregularly. Over half (57.6%, 113) of the CCHS population queried will have an encounter with a CCHS specialist at least once a year. Of those, 16.8% (33) will see the CCHS specialist 3 or more times a year.

Home Monitoring and Nursing Support in CCHS

The bulk of medical care for CCHS children takes place in the home setting and involves careful and constant vigilance in monitoring the child's health status. Data from this survey of 196 CCHS patients and their families

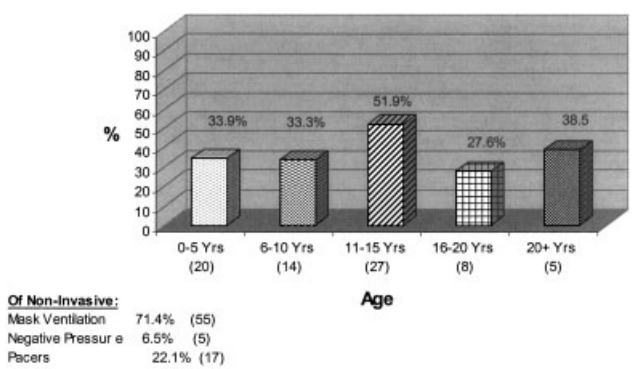

Fig. 3. Age profile of noninvasive ventilation: percent/age group (n = 75, 2 missing).

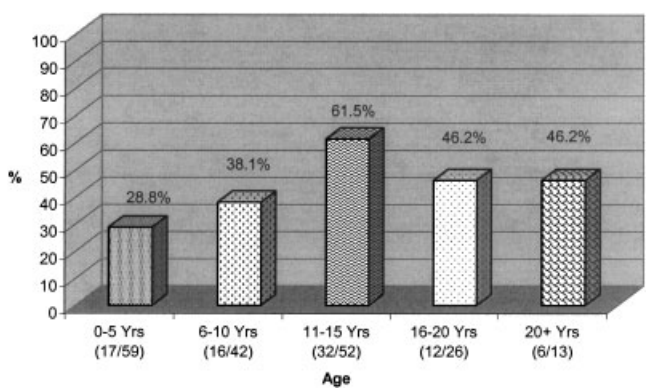

Fig. 5. Conscious breathing in CCHS (n = 196): percent of subjects who cued themselves, or were cued by others to take additional breaths.

TABLE 3— Frequency of Medical Tests in 196 CCHS Patients[1]

	Annually			Irregularly			Not in 5 years			Not since initial hospital discharge		
	Total	S-O (%)	24-hr	Total	S-O (%)	24-hr	Total	S-O (%)	24-hr	Total	S-O (%)	24-hr
Polysomnography	42	42	50	37	38	30	9	10	0	9	8	20
ECG	38	37	50	38	38	40				19	21	5
Echocardiogram	47	44	70	31	31	30				18	20	0
Bronchoscopy	15	11	45	34	34	35	18	19	10	31	33	10
24-hr Holter	17	15	40	27	28	20				53	55	35
Chest X-ray	24	22	40	60	60	60				13	15	0
Pulmonary function test	23	21	40	39	38	45				33	36	10
Eye/vision examination	55	53	65	30	30	30				13	14	5
Neuro assessment	25	22	50	38	38	40				34	37	5

[1]Values are rounded to nearest whole percent; Total, all 196 patients; S-O, mechanical ventilation only during sleep; 24-hr, mechanical ventilation all day.

provide a picture of a lifestyle dictated in large part by the care of these medically complex children. In addition to observing and caring for the child (including coordinating medical procedures, homecare practice, and health assessment with the primary physician and other medical professionals), parents must be attentive to the routine maintenance of sophisticated medical equipment in their homes. When there is nursing support, coordination and oversight of that care also fall upon the caregivers in the home.

Table 6 shows the presence of medical equipment and supplies in the households of CCHS patients, i.e., equipment in addition to the patient's mechanical ventilation system. Pulse oximetry monitoring is performed at home by 85.7% (168) of CCHS families, with 71.4% (140) of this group employing oxyhemoglobin saturation monitoring (and responding to alarms) at least nightly and while the child sleeps. Nearly half of these families also spot-check the CCHS child's oxyhemoglobin saturation status sometime during the day. About 4.0% (3.6%, 7) of families use the oximeter weekly to conduct spot checks, and another 6.1% (12) of caregivers use the pulse oximeter monthly or less often to check the respiratory status of their child. Alarm settings for low saturation varied among pulse oximeter users, with 14.3% (28) setting the alarm at 95% saturation or higher, 42.9% using 90%, and 25.0% (49) of families setting the alarm below 90%. Available supplemental oxygen is maintained in 67.9% (133) of CCHS homes for use during illness.

Fewer caregivers or CCHS patients routinely monitor CO_2 levels. While 42.9% (84) CCHS families have a CO_2 monitor at home, only 26.0% (51) use the device at least nightly. Ten families (5.1%) with CO_2 monitors reported weekly use to spot-check CO_2 levels during waking hours or while asleep, and 12.2% of families (24) spot-checked CO_2 levels monthly or less often. The majority of home CO_2 monitor users set the high CO_2 alarm at 46–55 mmHg, while over half of the remaining users set the alarm limit at >55 mmHg.

Backup ventilators were present in 60.2% (118) of CCHS homes, while over two-thirds (68.1%, 133) of all respondents reported experiencing a ventilator (or diaphragm pacer) malfunction at home. Further reflecting the stress that accompanies the home care and daily

TABLE 4— Number of Annual Hospital Admissions by Age in 180 CCHS Patients (n = 180; S-O = 160; 24-hr = 20)[1]

	Birth to 5 yrs n = 54			6–10 yrs n = 40			11–15 yrs n = 47			16–20 yrs n = 23			20 yrs n = 13		
HA	T	S-O	24-hr	T	S-O	24-hr	T	S-O	24-hr	T	S-O	24-hr	T	S-O	24-hr
0 %	33.3	37.5	0.0	47.5	50.0	33.3	59.6	63.6	0.0	69.6	71.4	50.0	46.2	41.7	100.0
(n)	(18)	(18)	(0)	(19)	(17)	(2)	(28)	(28)	(0)	(16)	(15)	(1)	(6)	(5)	(1)
1 %	33.3	33.3	33.3	35.0	38.2	16.7	31.9	31.8	33.3	13.0	14.3	0.0	7.7	8.3	0.0
(n)	(18)	(16)	(2)	(14)	(13)	(1)	(15)	(14)	(1)	(3)	(3)	(0)	(1)	(1)	(0)
≥2 %	33.3	29.2	66.7	17.5	11.8	50.0	8.5	4.5	66.7	17.4	14.3	50.0	46.2	50.0	0.0
(n)	(18)	(14)	(4)	(7)	(4)	(3)	(4)	(2)	(2)	(4)	(3)	(1)	(6)	(6)	(0)

[1]HA, hospital admissions/year; T, 180 patients for whom data are available; S-O, mechanical ventilation only during sleep; 24-hr, mechanical ventilation all day; yrs, years.

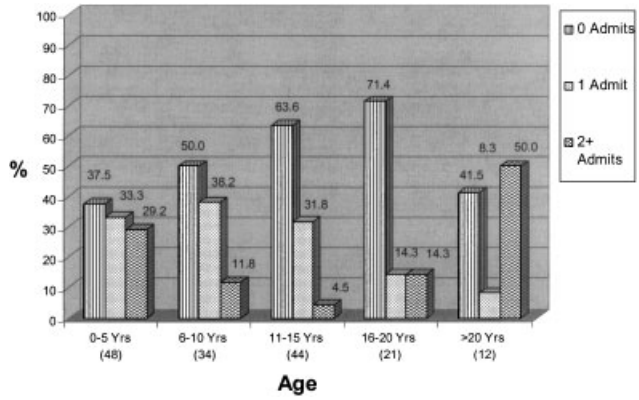

Fig. 6. Annual hospitalizations in 160 sleep-only ventilated CCHS patients (n = 160; 0 admits, 1 admit, and 2 or more admits).

respiratory support of CCHS children, 75.0% (147) of parents reported that they ''sometimes'' or ''always'' worried about ventilator system failure at home.

Nursing

Nursing support in the home can significantly lighten the healthcare burden for families with medically fragile and technology-dependent children. We queried the CCHS population about the degree of nursing support available to them. Figures 8 and 9 depict the home nursing situation among subgroups of the CCHS population. Half of the families reporting (49.5%, 97) had no nursing support at night, and 71.9% (141) had no daytime nursing support. Of those with nursing support at night, 50.0% (46) had 25–60 hr of nursing available, and 48.9% had >60 hr of night nursing during the week allocated to them by medical insurers or public programs. When asked whether they had adequate nursing hours available to them, 44.9% (88) of families responded in the affirmative. However, 50.5% (99 families) had no nursing support or reported that they did not have enough nursing support to allow them to optimize the care of their children.

Of families with school-age CCHS children, 63.5% (94) reported having no individual nursing support at school. Indeed, many parents (39.9%, 59) reported being on call to provide care for their children while they were at school. Other families (33.1%, 49) relied on the school nurse to care for any special needs of their child during school hours. A small number of families (4.1%, 8) selected to home school their CCHS child because of nursing issues. There were differences in the level of nursing support among CCHS children requiring 24-hr mechanical ventilation or only while asleep:

For example, only 10% of 24-hr ventilator-dependent CCHS children were without nighttime nursing hours, and in the same group, 60% of children had their own nurse to accompany and monitor them at school, i.e., during daytime hours away from home.

Family Stress and Lifestyle Issues

This survey also sought to obtain information on the perceptions of caregivers on the impact of CCHS home-care on family life, parenting, and family lifestyle. Table 7 reports parental responses on a range of issues that characterize several of the stresses CCHS families face as they adapt to the presence of a technology-dependent, medically complex child in the home. Parents and siblings of the CCHS child were affected by the family's pursuit of an optimized medical outcome for the CCHS child. Marital or relationship stability, decisions about having additional children, planning family vacations or social outings, and diminished opportunities for caregivers' career or educational advancement were among the issues CCHS families reported as struggling with. Parents also tended to lack full confidence in the healthcare advice of medical professionals and to worry about the degree of medical and financial support available to them, even as they spent considerable time coordinating their child's care.

Nevertheless, despite lifestyle changes and sacrifices made, parents appear to be highly motivated to provide

TABLE 5— Numbers of Annual Physician Visits by Age Among 174 CCHS Patients (n = 174; S-O = 157; 24-hr = 17)[1]

	Birth to 5 yrs (52)			6–10 yrs (37)			11–15 yrs (50)			16–20 yrs (23)			>20 yrs (12)		
Visits	T	S-O	24-hr	T	S-O	24-hr	T	S-O	24-hr	T	S-O	24-hr	T	S-O	24-hr
0–3 %	23.1	26.1	0	32.4	38.7	0	40.0	42.6	0	39.1	40.9	0	33.3	27.3	100.0
(n)	(12)	(12)	(0)	(12)	(12)	(0)	(20)	(20)	(0)	(9)	(9)	(0)	(4)	(3)	(1)
4–6 %	17.3	17.4	16.7	32.4	35.5	16.7	50.0	48.9	66.7	17.4	18.2	0	25.0	27.3	0
(n)	(9)	(8)	(1)	(12)	(11)	(1)	(25)	(23)	(2)	(4)	(4)	(0)	(3)	(3)	(0)
7–9 %	11.5	10.9	16.7	10.8	9.7	16.7	0	0	0	21.7	22.7	0	8.3	9.1	0
(n)	(6)	(5)	(1)	(4)	(3)	(1)	(0)	(0)	(0)	(5)	(5)	(0)	(1)	(1)	(0)
10+ %	48.1	45.7	66.7	24.3	16.1	66.7	10.0	8.5	33.3	21.7	18.2	100.0	33.3	36.4	0
(n)	(25)	(21)	(4)	(9)	(5)	(4)	(5)	(4)	(1)	(5)	(4)	(1)	(4)	(4)	(0)

[1]T, all 176 patients for whom there are data; S-O, mechanical ventilation only during sleep; 24-hr, mechanical ventilation all day; yrs, years.

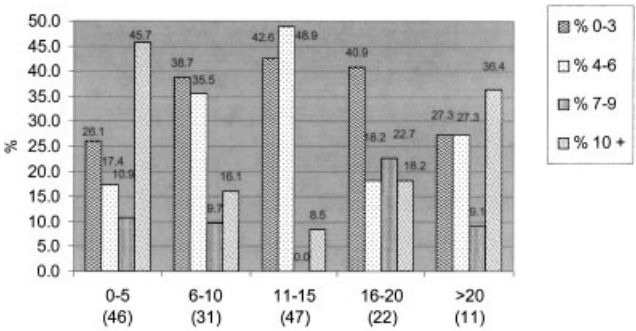

Fig. 7. Annual physician visits in 154 sleep-only ventilated CCHS patients (0–3 visits, 4–6 visits, 7–9 visits, and 10 or more visits).

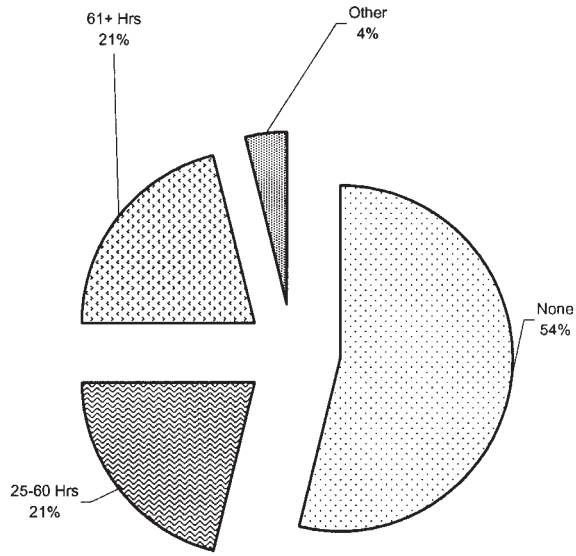

Fig. 8. Night nursing support: number of hours weekly.

home care for their child. Indeed, 78.1% (153) of the families believed that they provided better care for their child at home than the care their child would receive at a hospital. Furthermore, a majority of families (88.3%) stated that care for their CCHS child had become easier over time.

Families' Information on CCHS

Key to the provision of quality care, parental or patient confidence in prescribed medical regimen, and ultimate success for CCHS children and their families is timely information about the disorder and its treatment. Table 8 reports on sources of information to the families and on the issues families are likely to require more information on. Topping the list of sources relied upon by CCHS families around the world for information was the *CCHS Family Newsletter*, a biannual newsletter produced and distributed internationally by the CCHS Network, Inc., a parent-operated, not-for-profit organization in the United States. This publication reports on medical research in CCHS, on new technologies and ventilatory support options, and on home-care strategies developed by families. In addition, physicians and other CCHS parents were also key sources of information for CCHS families, while nearly a quarter of the parents (22.4%) reported that they consulted medical journals as specific medical issues developed. When asked about the type of information parents lacked or sought, CCHS parents most often cited information about the long-term prognosis in CCHS, and information on independent living options for those approaching their adult years. Nearly half of the families (48.5%) sought more information on issues that they should be aware of regarding their children, and nearly as many sought more information on options in ventilation (45.9%) and on optimal care regimes (42.3%). Fewer than 9% of families responded that they had enough information or knew where they could find the information they needed.

CCHS Children at School

Responses on the learning and school survey items indicated that 61.4% (94) of school-age CCHS children (n = 153) were in the regular classroom full time, while another 7.8% (12) were in the regular classroom most of the time (Table 8). However, 19% (29) of CCHS students were in a special-education classroom full time, with

TABLE 6— Medical Equipment and Supplies at Home in 196 CCHS Patients

Pulse oximeter	85.5%	168 (71.4% use at least nightly)
CO_2 monitor	42.9%	84 (26.0% use at least nightly)
O_2 supply	67.9%	133
Backup ventilator	60.2%	118 (61.8% have had ventilator/ pacer malfunction at home)
Suction machine	65.3%	128
Speaking valve	31.6%	62
Nebulizer	52.0%	102
Cardiorespiratory monitor	7.7%	15

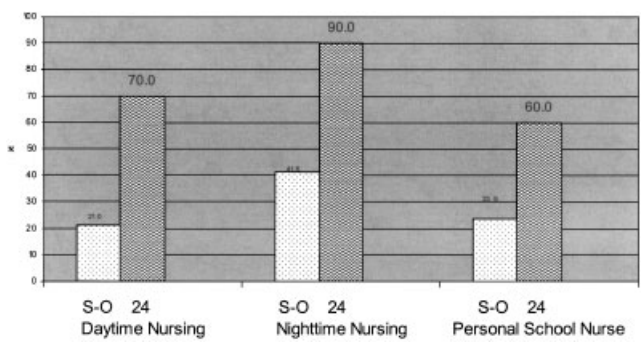

Fig. 9. Percent of families with nursing support (n = 196).

TABLE 7— Family Stress and Lifestyle Issues in 196 CCHS Patients: Issues at Present or in Past

"Child's health and care requirements have. . ."	%	n
Led to marital/relationship stress	60.2	118
Led to separation or divorce	15.8	31
Affected the decision to have more children	50.5	99
Led to stress for siblings of CCHS children	42.3	83
Led to behavior problems for siblings	25.5	50
Affected family vacations/recreation	75.5	148
Limited parents' social outings	73.5	144
Limited parents' occupational or educational mobility	66.8	131
Led to regularly canceling family events	31.6	62
Limited family's ability to use air travel	39.8	78
Required 5+ hr/month of care coordination and advocacy with service providers	27.6	54
Required up to 5 hr a month for coordination/advocacy	27.6	54
Led to worry about ventilator malfunction	75.0	147
Led to worry about continued financial support for CCHS medical care	54.6	107
Led to lack of full confidence in advice of primary-care provider	49.0	96
Led to lack of confidence in a covering physician's care/advice	81.6	160
Led to concern about unaddressed medical needs	11.2	22
Led to worry about inadequate local emergency care	28.1	55

another 7.1% (11) receiving special education most of the time. A significant number of CCHS schoolchildren had to repeat a grade (30.7%, 47).

While 63.4% of caregivers reported that their CCHS child "has problems learning," this group included both those children with and those without diagnosed learning disabilities. A quarter (24.7%, 24) of these respondents reported that their child had difficulties with reading and comprehension, while 20.6% (21) reported that math and/or spatial concepts were difficult for their child. An equal-sized group of parents reported that their child had trouble learning in several subject areas, sometimes complicated by behavioral issues such as attention deficits with or without hyperactivity (Table 8).

TABLE 8— CCHS Children at School (n = 153, School-Age Children or Graduates)[1]

Regular Classroom	%	(n)
Full time	61.4	94
Most of time	7.8	12
Half time or less	11.8	18
Special education classroom		
Full time	19.0	29
Most of time	7.1	11
Held back, repeated a grade: "has problems learning" (school-age, with and without LD diagnosis)	30.7	47
	63.4	97
Of those:		
Reading, comprehension	24.7	24
Math/spatial	20.6	21
ADD/ADHD	9.3	25
Several of these	20.6	20
Other	7.2	7
Missing	16.5	16

[1]LD, learning disability.

Physical Education Participation in School

An interesting question pertaining to the school years of CCHS children is whether they can or should be expected to participate in mainstream physical education (PE) curricula. Reasonable concern about the child's adequate respiratory response during the day and during exercise (while off mechanical ventilatory support or while relying on diaphragmatic pacing) would suggest that these children should be considered at-risk and therefore should be closely monitored when participating in any PE program.[16,17]

Figure 10 depicts the pattern of PE participation reported by CCHS parents of school-age or older children. A large majority of the children (62.7%) participated in PE programs without restrictions or modifications intended to reduce the possibility of respiratory decompensation. Less than a quarter of the children either had their own modified program or avoided contact sports.

Financial Support for CCHS Care

The medical and homecare requirements of CCHS children impose significant annual healthcare costs, such that few family incomes would cover or absorb these expenses yearly. Indeed, the survey revealed that both government-based programs and private insurers provided significant financial support to these children and their families. In 48.9% of CCHS households (n = 96), government programs provided for all or almost all of the child's medical costs. For nearly a quarter of the remaining families (24.0%, 47), private insurance covered all or almost all CCHS-related expenses. In 22.9% of families, healthcare costs were covered by a mix of government and private insurance programs. Only 2% of families (4)

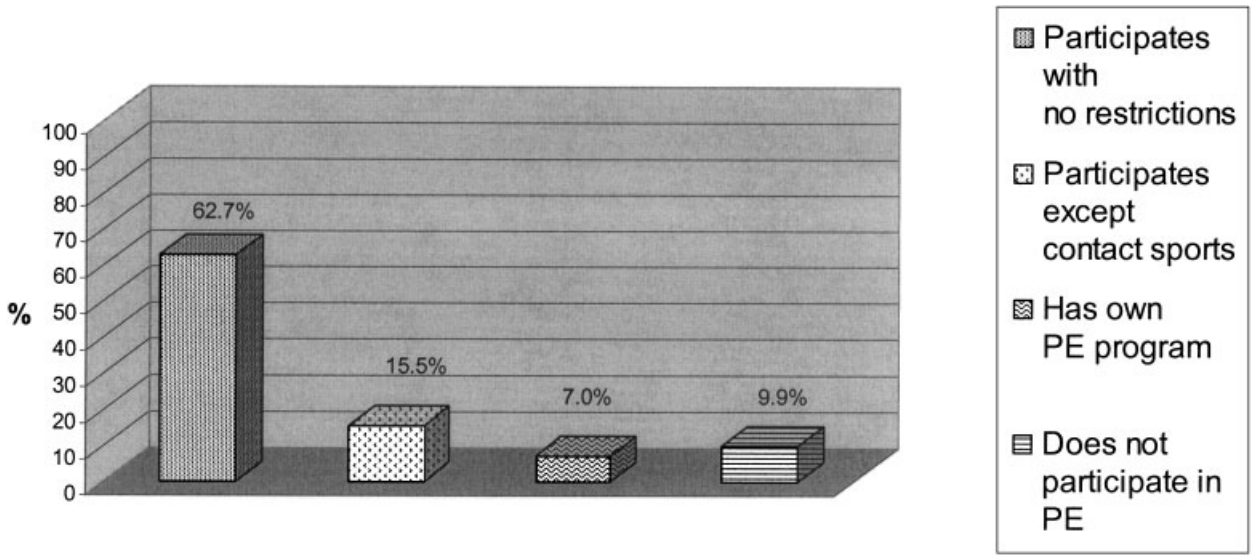

Fig. 10. Participation in PE at school (n = 142; 31.1% of children not in school, or does not apply).

reported that they had no outside financial support for their child's medical expenses.

As for the extent of medical coverage, 87.2% (171) of families had 76–100% of their child's health expenses covered by government and/or private insurance programs, 7.1% (14) had 51–75% of CCHS-related medical expenses covered, one family had support for less than 50% of their costs, and four families (2.0%) had none of their medical expenses covered.

Nevertheless, while financial support is ultimately available to most families, the need for caregiver advocacy for starting coverage and then ensuring continued coverage remains. As noted in Table 7, a majority of families worried about the continuation of financial support for their child's needs into the future. Moreover, despite the fact that current levels of healthcare intervention were largely funded, family or physician advocacy was typically necessary to increase the likelihood that medical evaluations or home nursing would be funded, or that new or replacement durable medical equipment would be provided.

DISCUSSION

The major findings of this study encompassing 196 CCHS patients and their families include a comprehensive delineation of the multisystem involvement that characterizes the CCHS phenotype, the evolution of mechanical ventilatory support modalities, the age-dependent acuity of disease and transition to the home setting, the inconsistency in periodic and regular medical management, and the substantial burden that the disorder imposes on families and the healthcare system.

Before we address some of these findings, some methodological issues deserve comment. First, this survey only targeted those CCHS children registered with a family network in their own countries. We may have missed relevant information on CCHS children who are not part of these family networks, and who therefore may present increased difficulties in coping with home and medical care. Thus, although the current survey depicts a cross-sectional overview of the largest population of CCHS patients studied thus far, it may have skewed some of the information towards that provided by more and better-informed parents. Secondly, we did not and could not obtain information on CCHS children who receive institutionalized care, and whose parents do not belong to one of the family networks. Thus, more severely affected patients, such as those with extensive neurocristopathies, may have been underrepresented in this study. Similarly, some of the information collected on the value of the Family Network would also be skewed towards more favorable responses by virtue of aforementioned considerations. Thirdly, while we could not verify that the diagnosis of CCHS among all responders was indeed achieved only after all tests delineated in the consensus criteria were performed,[3,15] the overwhelming majority of these children did undergo extensive medical evaluations by CCHS specialists.

The multidisciplinary needs of caring for CCHS patients clearly emerged in this survey (Table 1). However, the relative scarcity of multidisciplinary care as provided by teams consisting of pediatricians, pulmonologists, cardiologists, surgeons, gastroenterologists, neurologists, ophthalmologists, and psychiatrists, alongside social workers, nurses, speech and physical therapists, and special education teachers, seems to detract from achieving optimal care plans for these children. Ideally, these well-informed medical professionals, as well as the local

medical emergency unit and the home-care supply company, would work in a seamlessly integrated fashion with parent-caregivers to coordinate ongoing care and support the use of medical technologies in the home. Such is not the case for most CCHS families, and it is likely that the paucity of such multidisciplinary approaches merely reflects the small number of patients attending any given tertiary medical center. In fact, this survey also suggests significant gaps in the care of CCHS children that can and should be targeted for improvement. For example, the health management regimen suggested as optimal by a panel of CCHS experts[15] is not being routinely implemented. A sizable number of CCHS patients reported ''never'' or ''irregularly'' seeing a CCHS specialist, and obtaining a polysomnographic study, bronchoscopic assessment, or cardiac evaluation (Table 3). Given the risk for serious cardiac involvement in this disorder, potentially requiring implantation of cardiac pacemakers,[6] it is notable that many CCHS patients did not undergo routine Holter monitoring and other noninvasive evaluations. However, we should also emphasize that despite the large number of CCHS patients surveyed, the complexity of their disorder and the multiple outcome measures that need to be incorporated in a multivariate analysis precluded assessment of the intrinsic added value of periodic evaluation by a CCHS specialist.

This survey indicates that there are multiple obstacles to home discharge in this group of children, with only less than half of the children being discharged by age 7 months. This is similar to the length of hospitalization from which ventilator-assisted children were initially discharged (172 ± 161 days SD), as previously reported in 54 children requiring mechanical ventilation for a variety of medical reasons.[18] Furthermore, multiple hospitalizations and physician encounters occurred during the first years of life, suggesting that this is a particularly vulnerable period of the disorder. As would be expected from the complexity of their medical problems, CCHS children with Hirschsprung's disease and CCHS children who need 24-hr ventilatory support are more likely to require more frequent physician contacts, hospital admissions, and medical interventions over time.

We found that 39% of CCHS children overall were using noninvasive ventilatory support, i.e., without tracheotomy, and that, in general, the process of transitioning to noninvasive ventilation occurred after age 6 years and included several children who were 24-hr ventilator-dependent. In fact, 14.3% of the children were never tracheotomized, and a third of the children on nasal mask bilevel positive-pressure ventilation had switched to this mode of ventilatory support before age 5, reflecting the increasing tendency to achieve this type of mechanical ventilation earlier in life.[19] It remains unclear, however, whether children who never received mechanical ventilatory support via a tracheostomy fared differently from those who underwent invasive mechanical ventilation early in life. Since current practices in the US and other countries are very diverse, it would be important to compare the overall outcome and disease characteristics of children receiving noninvasive ventilatory support from birth to those who were tracheotomized and ventilated for at least their first few years of life.

At the other level of care for CCHS children, the home setting, families responding to this survey identified several areas where they felt they needed better support. Indeed, a significant number of CCHS homes were not equipped with appropriate monitoring or medical equipment such as backup ventilators, capnographs, and supplemental oxygen. Fifteen percent did not have oxyhemoglobin saturation monitors, even though these devices are considered standard for home care by discharging physicians who are CCHS specialists. The needs for home equipment appear all the more pressing in light of the less-than-optimal frequency of medical evaluations and the generally limited availability of nursing support for family care providers. While the family reporters in this survey appeared highly motivated to care for their children at home, they were often providing such care without the benefit of a robust support system by medical and/or home-care professionals. While we are uncertain as to the multifactorial components leading to the relatively inadequate preventive care in CCHS patients, it is likely that increased awareness by both parents and primary-care physicians will increase advocacy for more vigilant monitoring, and improved support from public or private funding sources for medical support and periodic evaluation, home equipment, and nursing.

This survey further supports the concept that it is extremely difficult for CCHS parents to achieve the necessary arrangements to provide adequate care for their children while they attend school. Indeed, only a minority of these medically complex children reported individual nursing support at school or regular monitoring by trained personnel in school, in particular during PE programs or at recess, when the likelihood of respiratory compromise may be greatest. While many CCHS children may tolerate moderate, age-appropriate physical activity, they lack appropriate autonomic responses during heavy or extended exercise.[16] Moreover, under some circumstances, exercise could interfere with the diaphragmatic pacer ventilation in use by children requiring 24-hr ventilatory support.[13]

Although CCHS children face numerous challenges and are prone to medical compromise, a majority have succeeded or are currently succeeding in academics. Nearly two-thirds make normal progress in regular classrooms, although over a quarter of CCHS children have been held back a grade. Further, most have had speech and/or physical therapy at some time in their lives,

and, many parents stated that their child had learning difficulties in one or several subject areas. Less than a quarter of CCHS children work in special-education classrooms all or part of the time. Overall, although most CCHS children will require academic and/or developmental support services of some kind during their school years, the overall outcome is clearly favorable.[12,20]

Finally, this survey confirms a central role for parents and families who monitor their CCHS children 24 hr a day, who maintain vans and other transport equipped with resuscitation bags, oxygen, and/or ventilators, and who organize family life around the needs of their special children. The extent of the healthcare burden carried by these highly motivated parents is reflected both in the stress they report, and in the fact that the parents coordinate and undertake most of their child's complex care, and serve as advocates for services. It would therefore seem appropriate that community-based healthcare and support services play a more active role to assist CCHS families in meeting the challenges involved in providing optimal care for such complex patients.

In summary, this comprehensive survey of 196 CCHS children and their families provides a cross-sectional picture of the multifaceted complexities associated with this disorder, and points to substantial inadequacies associated with their routine preventive care that appear to impose substantial stress to the families. The emerging trend of an earlier transition to noninvasive ventilatory support warrants a more structured and objective study aiming to examine the implications of such an approach. Similarly, widespread incorporation of the recently published recommended guidelines for diagnosis and multidisciplinary follow-up of CCHS patients, along with improved organization of support services to patients and their families, should ultimately ameliorate the long-term outcome of this lifelong condition.

ACKNOWLEDGMENTS

The authors acknowledge the language-translation support provided by Almos Cseke, M.D. (Germany), Cristina Labardi Risaliti, M.D. (Italy), Paul-Emile LaFleur (France), and Dolores Arrebola Diaz (Spain).

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