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Congenital Central Hypoventilation Syndrome (CCHS): Patient Quality of Life and Caregiver Burden

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ABSTRACT

Background: Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder characterized by autonomic dysregulation and abnormal control of breathing, necessitating lifelong artificial ventilation. The impact of CCHS on patient quality of life (QoL) and caregiver burden remains unquantified.

Methods: A cross-sectional study of QoL in CCHS patients (≥ 12 years; WHOQOL–BREF) and burden in CCHS caregivers (Zarit Burden Interview) was conducted. Participants were recruited from CCHS support organizations. Participant age group, sex, primary language, and country of residence were collected.

Results: Two hundred seventy-one individuals (78 CCHS, 193 caregivers) from 15 countries participated. CCHS patients reported significantly reduced physical, psychological, and social relationships domain scores compared to healthy controls ($p < 0.01$), yet > 70% reported good overall QoL. Over half reported moderate or worse impact on QoL items including medical treatment dependence and cognitive function. Young CCHS patients (< 25 years) reported better overall QoL and general health than those ≥ 25 years. CCHS caregiver burden was increased compared to that reported in other chronic diseases, with > 50% reporting frequent caregiving-induced stress. Caregivers who reported financial issues also reported higher total burden ($p < 0.05$).

Conclusions: CCHS QoL scores are depressed compared to healthy individuals. This study identified specific domains of QoL and caregiver burden most impacted by CCHS, revealed a relationship between age and QoL in CCHS, and finances and burden in caregivers. Results offer targets for future interventions to enhance QoL in CCHS and reduce caregiver burden. Further work is needed to elucidate the relationship between CCHS impact and disease- and treatment-specific factors.

1 | Introduction

Congenital Central Hypoventilation Syndrome (CCHS; OMIM: 209880) is a rare disorder of neural crest origin characterized by hypoventilation during sleep, and in more severe cases during sleep and wakefulness, necessitating artificial ventilation as life-support. Affected individuals lack normal central and peripheral chemo-responsiveness, leading to markedly attenuated control of breathing. Caused by heterozygous paired-like homeobox *(PHOX2B)* gene variations, children typically present in the

newborn period. The phenotype typically also includes variably diffuse impairment of autonomic nervous system (ANS) development and function, including altered gastrointestinal motility (with and without Hirschsprung disease [1, 2]), cardiovascular regulation (abrupt sinus pauses, orthostatic hypotension [3–5]), and tumors of neural crest origin [2], amongst others.

Although initially described in 1970 [6], increased awareness of CCHS coupled with the introduction of genetic testing for *PHOX2B* gene variants in 2003 [7, 8] led to improved identification and care. Before this, prognosis was poor with a reported mortality rate of 38% and a median age of death at 3 months [1]. Presently, patients with CCHS typically reach well into adulthood with multi-disciplinary care, with a recent study showing early mortality $< 4\%$ in a cohort receiving care at a CCHS referral center [9]. These improved outcomes appear to be related to coordinated, multidisciplinary management and regular specialist evaluations to optimize care and quickly identify coexisting conditions [10, 11]. Indeed, advances in diagnosis, now typically in the first months of life, and developments in care have reduced morbidity and mortality [1, 12].

While life expectancy and clinical outcomes are improving for individuals with CCHS, the control of breathing deficit and need for artificial ventilation persist throughout life. Options vary for mode of artificial ventilation and length of use (from night-only up to 24-h/day) depending on clinical need. Beyond artificial ventilatory support, therapeutic interventions are lacking. There is a considerable care burden forced upon families of technology-dependent individuals with CCHS, as well as the pediatric and adult patients themselves, who necessitate continuous vigilant management. Optimized outcomes typically require rigorous coordination between families, community practitioners, local hospitals, and national referral centers to synchronize and personalize care. By necessity, the family, patient, and home and/or school nurses must become expert in CCHS, airway management, home monitoring of oxygenation and ventilation, taking on a central role in keeping the CCHS patient at home, while also coping with everyday life issues.

An understanding of the impact of CCHS and management decisions on patient quality of life (QoL) and caregiver burden are critical to advance consensus care in CCHS, advocate for critical resources and support for CCHS families, and develop therapeutics targeted at meaningful outcomes. Although an early report briefly described the impact of CCHS on family stress and lifestyle [13], it was without *PHOX2B* variant-confirmation, included predominately US families, and was conducted over 20 years ago when the clinical picture of CCHS varied significantly from today. To our knowledge, there are no published studies specifically measuring QoL among *PHOX2B* variant-confirmed individuals with CCHS, and assessments on the impact of CCHS on families and caregivers are limited. As CCHS is an ultra-rare disorder, global cooperation is required to capture data reflective of the broader CCHS population and to establish a robust foundation of knowledge of the impact of CCHS and management decisions on QoL and caregiver burden. Consequently, the purpose of this study was to assess and describe the impact of CCHS on patient QoL and caregiver burden by utilizing well-validated and widely translated instruments to objectively characterize health-related QoL and caregiver perceptions of burden in an international cohort of individuals with CCHS and caregivers [14, 15].

2 | Materials and Methods

2.1 | Study Design

This is a cross-sectional, international questionnaire study conducted in individuals with *PHOX2B* variant-confirmed CCHS and their primary caregivers. The study was conducted in accordance with the Declaration of Helsinki and approved by a French ethics committee (Comité d'éthique de la Société de Réanimation de Langue Française SRLF – CE SRLF 23-051). Before participation, all persons involved had to provide their informed consent for inclusion in the study.

2.2 | Inclusion/Exclusion Criteria

2.2.1 | CCHS

Children 12 years and older with *PHOX2B* variant-confirmed CCHS were included. Those < 12 years of age were excluded due to lack of questionnaire availability in this age category.

2.2.2 | Primary Caregivers

Primary caregivers of individuals with CCHS, regardless of the age of individual receiving care, were included. Primary caregiver was defined as "the person who comes to the aid, on a regular and frequent basis, in a nonprofessional capacity, to perform all or part of the acts or activities of daily living of a person affected by CCHS."

2.3 | Study Recruitment

CCHS family support organizations in France, Germany, Israel, Italy, Poland, Portugal, Spain, the United Kingdom, and the United States participated in recruitment. Importantly, many of these organizations have involvement with families with a CCHS diagnosis living outside the country they represent. Anonymous SurveyMonkey links were made available between September 25 and December 2, 2023 by email contact lists of the support organizations. In addition, the global United States-based CCHS Network used their private Facebook page, "The CCHS Family Network," to inform the CCHS community of this research. Facebook page access to this network is restricted to confirmed CCHS patients and their families with a physician-reviewed record.

All data collected were anonymous. Beyond the validated questionnaires (described below) additional questions were limited to age, sex, home country, and primary language. Questions were limited to remain compliant with national regulations. Race and ethnicity were not collected due to national restrictions. No questions were mandatory except consent. There was no financial incentive to participate.

2.4 | Questionnaire Instruments

Validated questionnaires were chosen based on recognition by the international scientific community, adaptation of the questionnaire to the cultures of the anticipated participants, and the availability of well-validated translations.

2.4.1 | WHOQOL Questionnaire (for Individuals With CCHS)

The World Health Organization QOL–BREF (WHOQOL-BREF) is a 26-item generic questionnaire based upon a conceptualization of QoL as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, standards, expectations, and concerns [16]. WHOQOL-BREF includes two benchmark items that are meant to reflect overall health-related QoL (Overall QoL) and general satisfaction with health (General Health). The other 24 questions are mapped to four domains including physical health, psychological health, social relationships, and environment, as recommended by the developers [16]. Each item on this questionnaire is scored 1–5 and the total score is transformed to a scale of 0–100 for each domain, with lower scores representing more severe impact on QoL. Presently, the WHOQOL-BREF is available in 50 languages [17].

2.4.2 | Zarit Burden Interview (ZBI) (for Primary Caregivers)

This questionnaire contains 22 items scored on a 5-point Likert scale. These 22 items, each scored 0–4, are summed to create a total score ranging from 0 to 88, with higher scores representing increased reported burden. The questions investigate the perceived consequences of acting as a primary caregiver for a family member with a medical condition, and map to five domains including the impact of caregiving on control over one's life (four items), psychological well-being (seven items), finances (one item), social and family life (four items), and relationship between the caregiver and care-receiver (six items) [15, 18]. In keeping with published literature, scores of ≤ 20, 21–40, 41–60, and ≥ 61 were considered to indicate no, mild, moderate, and severe burden, respectively [19]. ZBI is currently available in over 100 languages [20].

2.5 | Data Analysis

A questionnaire with the minimum number of responses allowing scoring in accordance with the questionnaire administration and processing methodology defined by the World Health Organization (WHO) and the Mapi Research Trust was considered valid [17, 20].

Data were analyzed using IBM SPSS version 29 (Armonk, NY). Descriptive statistics were used to summarize data and histograms were used to examine distributions of continuous variables. The Chi-Square and Fisher's exact tests were used to compare categorical data. T-tests were used to compare the mean scores between two subgroups of the participants. Mann-Whitney U tests were used for non-parametric data, and for analysis of ordinal variables. One-way analysis of variance (ANOVA) and the Tukey post hoc test were used to compare means between three or more subgroups of the participants. Kruskal-Wallis H test was used for non-parametric testing of three or more groups. p-values (two-sided) were reported and considered significant at ≤ 0.05. Cronbach's α was used to assess internal consistency for each questionnaire and for previously established domains within each questionnaire, with values 0.7 and above being considered good. Correlations were assessed using Pearson's R or Spearman's rho (non-parametric and ordinal variables).

3 | Results

3.1 | CCHS and Primary Caregiver Cohorts and Questionnaire Responses

Overall, 271 participants completed valid survey responses between the WHOQOL-BREF and ZBI (Table 1). Participants represented 15 countries, primarily distributed across Europe and North America. Given the fully anonymous method of administration of the questionnaires, the specific number of patients and/or caregivers who received or saw the link to the questionnaire but did not respond cannot be quantified.

4 | By Specific Questionnaire

4.1 | WHOQOL-BREF (CCHS Patients)

A total of 129 responses to the WHOQOL-BREF were received, of which 78 were considered valid (60.5%). Among valid responses, 68 participants completed all 26 items, eight completed 25/26, and two completed 24/26. The majority of the 78 participants were from countries across Europe ($n = 64$, 82%), with individuals from the United States and Canada accounting for the remaining participants ($n = 12$, 15%, $n = 2$, 3%, respectively). Among respondents, 53% were female. Age groups ranged from the 12–18 years category to the 60+ years category. Frequencies of individual responses for the two benchmark questions (Overall QoL and General Health) and the 24 domain-specific questions are reported in Table 2.

4.1.1 | Benchmark Questions

4.1.1.1 | Overall QoL. Seventy-two percent of individuals with CCHS reported good or very good overall QoL (Table 3), with only 7% reporting poor QoL. A significantly higher proportion of pediatric and young adult individuals with CCHS (< 25 years of age) reported good or very good overall QoL compared to older individuals with CCHS (≥ 25 years of age, $p = 0.016$, Table 3).

4.1.1.2 | General Health. Half of individuals with CCHS reported being satisfied or very satisfied with their general health (Table 3). 15% expressed feeling dissatisfied or very dissatisfied.

TABLE 1 | Survey participants.

	Overall (271) % (N)	Patient (78) % (N)	Caregiver (193) % (N)
Sex			
Female	76 (207)	53 (41)	86 (166)
Male	20 (53)	41 (32)	11 (21)
Other/ Unreported	4 (11)	6 (5)	3 (6)
Age (years)			
12–18[a]	8 (21)	27 (21)	0 (0)
18–24[a]	8 (21)	24 (19)	1 (2)
25–34	17 (46)	22 (17)	15 (29)
35–49	44 (118)	13 (10)	56 (108)
50–59	16 (44)	4 (3)	21 (41)
60+	6 (15)	5 (4)	6 (11)
Unreported	2 (6)	5 (4)	1 (2)
Country of residence			
USA	20 (54)	15 (12)	22 (42)
France	17 (47)	19 (15)	17 (32)
Italy	14 (37)	15 (12)	13 (25)
Poland	13 (35)	17 (13)	11 (22)
Germany	10 (26)	13 (10)	8 (16)
Spain	7 (19)	5 (4)	8 (15)
United Kingdom	8 (23)	6 (5)	9 (18)
Portugal	4 (12)	5 (4)	4 (8)
Canada	2 (6)	3 (2)	2 (4)
Argentina	1 (3)	0 (0)	2 (3)
Belgium	1 (3)	0 (0)	2 (3)
Australia	1 (2)	0 (0)	1 (2)
Netherlands	1 (2)	1 (1)	1 (1)
Austria	0 (1)	0 (0)	1 (1)
Norway	0 (1)	0 (0)	1 (1)

[a]The survey included these age categories (18 years of age in two categories), which led to ambiguous categorization for those participants 18 years of age in the WHO-QOL.

Benchmark scores did not significantly differ by age group, gender, country or language.

4.1.2 | Domains

Average scaled scores for individuals with CCHS ranged from 56.9 to 66.0 (Table 4). Individuals with CCHS reported significantly reduced QoL in the physical, psychological, and social relationships domains compared to previously reported similarly aged healthy controls [14] (Table 4). Females reported higher scores in social relations domain than males (Means 62 vs. 51, $p = 0.04$ 95% CI 0.5–21). There were no other significant domain differences by age group, gender, country, or primary language. Several individual domain questions highlighted areas of specific concern in CCHS (Table 2).

4.1.3 | Data Reliability and Agreement

Internal consistency was good for the overall WHOQOL-BREF questionnaire (Cronbach's $\alpha = 0.93$). For the individual domains, it was also good for all domains ($\alpha > 0.75$), but moderate for the social relationships domain ($\alpha = 0.69$), similar to prior reports in large control populations [14]. Domains were significantly correlated with each other ($p < 0.001$) and with the benchmark questions (overall QoL and general health satisfaction; $p < 0.001$).

4.2 | Zarit Burden Interview (Caregivers)

For the caregiver questionnaire (ZBI), 217 caregivers provided responses, including 193 (88.9%) caregivers who completed all 23 items (Table 1). The majority of the ZBI participants were from countries across Europe (74%) and the United States (22%). Most (86%) of the respondents were female. Participating caregivers ranged in age from early adulthood to > 60 years of age. Frequencies of individual responses for the ZBI questions and mean cohort scores for each question are reported in Table 5.

4.2.1 | Overall Burden

The total level of burden reported by caregivers ranged from 0 to 79 (mean = 36.4, SD = 14.1). Using previously defined score categories, the majority of CCHS caregivers reported mild to moderate levels of burden (46% and 35%, respectively), with less than 4% reporting severe burden. Scores did not significantly differ by age group, sex, country or language.

4.2.2 | Domains

Scores were similar across all domains (Table 5). Average domain scores ranged from 1.5 (SD = 0.67, domain 2) to 1.8 (SD = 0.8, domain 1), where the average response score across all domains was 1.7 (SD = 0.64). Domain scores did not significantly differ by age group, sex, country or language. Several individual domain questions highlighted areas of specific concern in CCHS caregivers (**bold**, Table 5).

4.2.3 | Impact of Finances on Caregiver Burden

A single question on the ZBI assesses the impact of financial burden on caregivers. Caregivers are asked to assess how often they feel they do not have enough money to care for the individual with CCHS, in addition to other expenses with answers ranging from never to nearly always (Table 5). ANOVA testing showed a significant difference in overall ZBI reported caregiver burden based on the financial response (Figure 1). Those choosing "Never" to financial issues reported significantly

TABLE 2 | Frequency response (%) for items for the WHOQOL-BREF ($n = 78$).

Domains and questions (abbreviated)	1 (Poor QoL) %	2%	3%	4%	5 (Good QoL) %	Mean score
Overall QoL	1	6	19	56	17	3.8
General health Satisfaction	3	12	35	41	10	3.4
Domain 1 - Physical Health						**3.6**
Pain and discomfort	1	5	16	22	56	4.3
Dependence on medication[a]	33	0	22	21	24	3.0
Energy and fatigue	6	9	33	38	13	3.6
Mobility	6	10	19	21	44	3.6
Sleep and rest	9	6	32	42	10	3.2
Activities of daily living	3	13	22	35	28	3.6
Working capacity[a]	6	16	36	30	12	3.9
Domain 2 - Psychological						**3.6**
Positive feelings	3	8	27	53	10	3.4
Spirituality, religion and personal beliefs	6	9	24	38	22	3.6
Thinking, learning, memory and concentration[a]	3	18	47	26	6	3.4
Body image	1	15	26	35	23	3.7
Self-esteem	5	14	27	37	17	3.4
Negative feelings	1	19	23	45	12	3.8
Domain 3 - Social Relationships						**3.5**
Personal relations	6	8	26	42	18	3.4
Satisfaction with sex life[a]	14	14	41	18	13	3.7
Practical social support	5	12	31	32	21	3.2
Domain 4 - Environment						**3.6**
Physical safety and security	3	12	28	44	14	3.5
Physical environment	3	4	24	43	26	3.6
Financial resources	8	14	26	35	18	3.0
Information and skills	4	12	23	38	23	3.5
Recreation and leisure	10	12	26	32	21	4.2
Home environment	1	4	10	38	46	3.4
Access to health and social care	9	12	24	40	15	3.7
Transport	6	12	16	35	31	3.5

[a]Identified areas of concern in CCHS with ≥ 50% reporting score 3 or less.

lower total burden scores than all other subgroups (Tukey HSD $p < 0.05$). Those reporting "Nearly always" to financial issues reported significantly higher total burden scores than all other subgroups (Tukey HSD $p < 0.05$).

4.2.4 | Data Reliability and Agreement

Internal consistency was strong for the full ZBI questionnaire (Cronbach's $\alpha = 0.90$) and moderate for the individual domains (range $\alpha = 0.64$–0.075). Domains were significantly correlated with each other and with the total burden score ($p < 0.001$).

5 | Discussion

CCHS is a medically complex disorder, requiring a life-long dependence on artificial ventilation, and involving all organ systems served by the ANS leading to altered gastrointestinal motility, cardiovascular function, and diffuse autonomic dysregulation. Despite the anticipated impact of CCHS on patients and their families, no studies have previously assessed patient QoL and caregiver burden using objective, validated questionnaires. In this cross-sectional, questionnaire study, we report on patient responses to the WHOQOL–BREF and CCHS caregiver responses to the ZBI. Using the WHOQOL-BREF, the physical, psychological, and social relationship domains revealed significantly reduced QoL in CCHS patients compared to healthy

TABLE 3 | Overall quality of life and general health satisfaction in CCHS by age and sex.

	Group (N)				
		Age in years		Gender	
	All (78) %	< 25 (40) %	25+ (38) %	M (32) %	F (41) %
Overall quality of life					
Poor or Very poor	7	5	11	12	17
Neither poor nor good	21	13	29	4 1	32
Good or Very good	72	82	60	47	51
General health					
Dissatisfied or Very dissatisfied	15	11	19	12	5
Neither satisfied nor dissatisfied	35	37	31	19	21
Satisfied or Very satisfied	50	52	50	69	74

TABLE 4 | WHO-QOL domains in CCHS and healthy controls ages 12 +.

	CCHS ($N = 79$)		Healthy ($N = 3862$) [14]		Mean difference	Difference 95% CI	p-value[a]
	Mean	SD	Mean	SD			
Physical	63.6	20.0	71.3	18.1	7.7	3.7–11.8	< 0.001
Psychological	62.1	16.9	67.5	17.5	5.4	1.5–9.3	< 0.01
Social relationships	56.9	22.9	67.5	20.0	10.6	6.1–15.1	< 0.001
Environment	66.0	18.6	63.1	16.3	−2.9	−6.6–0.8	NS

[a]unpaired T-test.

controls. However, on the two benchmark questions, only 7% of individuals with CCHS reported poor/very poor overall QoL and only 15% reported dissatisfaction with their general health. On these questions, most individuals with CCHS reported good overall QoL and satisfaction with their general health. Younger individuals with CCHS reported higher overall QoL and general health satisfaction than those aged ≥ 25 years. With ZBI, most caregivers reported mild or moderate levels of burden with < 4% reporting severe burden. Caregivers who reported financial issues also reported significantly higher total burden scores. Overall, results identified specific areas of QoL that tend to be most impacted in CCHS, and highlighted areas of concern for caretakers of individuals with CCHS.

Interpreting our findings in CCHS is challenging due to a paucity of literature assessing QoL in individuals who are dependent on technology for home ventilatory support. Studies utilizing a variety of qualitative and quantitative methods in individuals with home mechanical ventilation have identified negative impacts on reported QoL [21–25]. One study, using PedsQL, found lower scores in pediatric patients with home ventilation compared to similarly aged healthy individuals on all assessed dimensions of QoL, including physical, psychological, social functioning, and emotional [21]. These results are in line with our finding of reduced QoL in the physical, psychosocial, social relationships domains of WHO-QOL BREF in CCHS. A recent scoping review highlights 10 publications assessing QoL in children and adolescents with home mechanical ventilation [24]. This study demonstrated a significant impact of home mechanical ventilation on perceived QoL. Of interest, findings revealed that reported QoL was dependent on when home ventilation was initiated and how long it had been used. Children who were on ventilation from infancy reported higher QoL, similar to healthy individuals, compared to those with later initiation of home ventilation. The authors hypothesized that those children with earlier onset had no memories of their lives before initiation of ventilatory support and were better adapted to their situation, reducing the impact on QoL. Similar to these early onset home ventilation individuals, CCHS is a congenital disorder, and most individuals with CCHS have home ventilatory support from infancy, throughout life [10, 11]. While WHO-QOL scores were depressed in CCHS, individuals with CCHS generally reported good QoL and health satisfaction on benchmark items, despite being technology-dependent and dealing with a chronic illness. It is possible that individuals with CCHS adapt more easily to their situation given typical disease onset in the first months of life (> 90% of CCHS). In our study, younger individuals with CCHS reported better overall QoL than older individuals. The cause of this finding is unclear, but may be due to improved identification and treatment of CCHS over the last 20 years, the requirement for older individuals with CCHS to care for themselves as they become adults, limited availability of holistic, multidisciplinary team-based care for adults with CCHS, a general relationship between age and reported QoL, or other, unknown factors.

While the primary morbidity of CCHS is the need for life-long ventilatory support, individuals with CCHS have a wide variety of additional morbidities, including gastrointestinal dysfunction.

TABLE 5 | Frequency response (%) for items in the Zarit Burden Interview ($n = 193$).

Domains and questions (abbreviated)	Never 0%	Rarely 1%	Sometimes 2%	Quite frequently 3%	Nearly always 4%	Mean score
Domain 1 - Burden in the relationship						1.8
Relative asks for more help than needed	38	25	23	9	4	1.2
Your relative is dependent on you[a]	2	4	17	29	49	3.2
Insufficient privacy because of your relative	14	19	31	22	15	2.0
Relative expects you to take care of him or her, as if you were the only one to depend on	31	15	22	20	13	1.7
Wish you could leave the care to someone else	49	17	27	6	2	0.9
Feel you should be doing more for your relative	11	26	36	18	9	1.9
Domain 2 - Emotional well-being						1.5
Not enough time for yourself	8	8	35	30	19	2.4
Embarrassed over behaviors	64	16	15	4	2	0.6
Angry when around your relative	51	31	15	3	1	0.7
Strained when around your relative	30	27	32	9	2	1.2
Your health has suffered because of caring	13	16	37	24	11	2.0
Could do a better job caring for your relative	16	31	36	11	7	1.6
Overall, how burdened do you feel in caring[b]	22	25	23	22	8	1.7
Domain 3 - Social and family life						1.6
Stressed between caring and other responsibilities[a]	5	8	29	35	23	2.6
Relative affects your relationship with others	39	22	29	7	2	1.1
Social life has suffered because of caring	11	16	26	24	23	2.3
Uncomfortable having friends over because of relative	68	18	10	2	3	0.5
Domain 4 - Finances						1.7
Do not have enough money to care for your relative	20	28	27	16	9	1.7
Domain 5 - Control over one's life						1.7
Afraid of what the future holds for relative[a]	1	3	18	36	42	3.2
Not able to take care of your relative much longer	53	23	17	5	3	0.8
Lost control of your life since your relative's illness	20	20	34	17	9	1.8
Uncertain about what to do about relative	37	29	25	7	2	1.1

[a]Identified as specific areas of concern in CCHS with ≥ 50% reporting score 3 or more.
[b]Item response categories for this question are not at all (0), a little, moderately, quite a bit, and extremely (5).

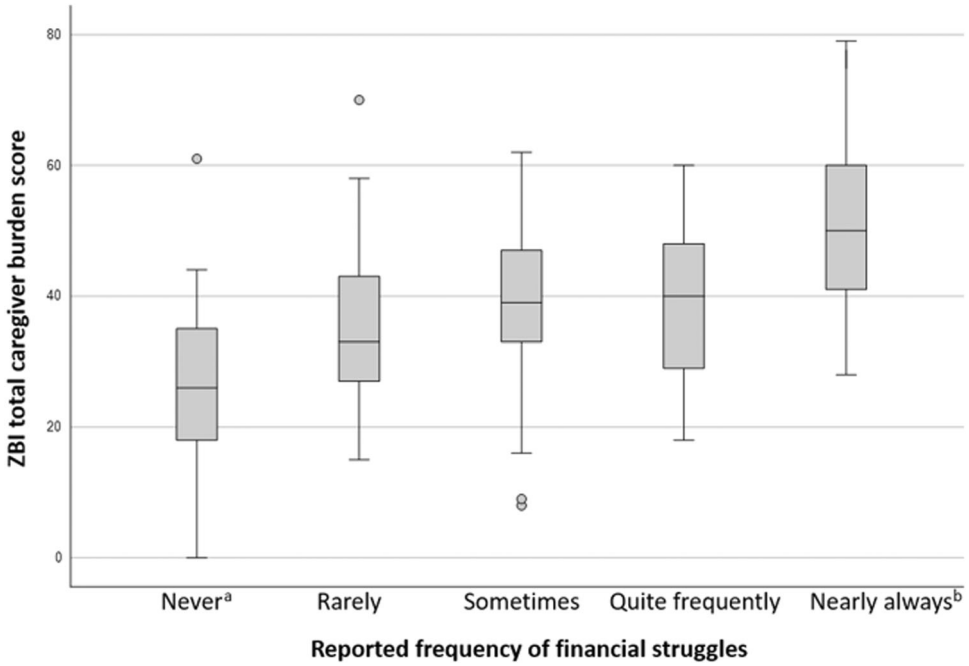

FIGURE 1 | [a]Those reporting "Never" had significantly lower total burden score than all other subgroups. [b]Those reporting "Nearly always" had significantly higher total burden score than all other subgroups.

Hirschsprung disease occurs in up to 20% of individuals with CCHS, and a large proportion of those without Hirschsprung report gastrointestinal dysmotility [10, 11]. Clinical observation indicates a large impact of gastrointestinal dysfunction on the lives of many individuals with CCHS. Prior studies have established a negative impact of Hirschsprung disease and gastrointestinal dysmotility on patient reported QoL, including a strong impact on the physical and psychological domains of QoL [26, 27], both of which were significantly reduced in CCHS individuals in our study. In the current study design, deciphering the impact of gastrointestinal dysmotility from reliance on home ventilation and other CCHS-related morbidities is not possible. Future work examining QoL in relation to CCHS disease manifestations will be critical to identifying targets most likely to improve QoL.

While we did not directly compare the ZBI results in CCHS caregivers to results reported in other populations, a recently completed large meta-analysis of how ZBI-reported caregiver burden correlates with the dependent's illness gives some context to our results. The analysis included 125 published studies [28]. Results demonstrated that caregivers of those with physical disabilities (e.g., Parkinson's disease, multiple sclerosis) report average ZBI scores ($\pm$SE) of 27 ± 2.6. This score was significantly lower than those identified in caregivers of those with mental disorders including cognitive impairment (34.1 ± 1.1), mental illness (32.6 ± 1.7), and Alzheimer's (32.5 ± 1). In our study, caregivers of individuals with CCHS reported ZBI scores of 36.4 ± 1.0. This indicates the caregivers of CCHS are likely experiencing substantially higher burden than reported in other, even serious, physical diseases, and an overall burden that may be increased even compared to caregivers for individuals with severe mental disorders. A 2004 study assessed stress and lifestyle issues in CCHS families [13]. In that study, significant financial and psychosocial burden were reported by family members of individuals with CCHS. Our study also identified areas of psychosocial burden in CCHS caregivers (Table 5), including frequent reports of stress similar to those identified in the 2004 study. In our study, a relationship between reported caregiver burden and finances was apparent. The relationship between finances and caregiver burden here are in line with a recent study that identified a strong correlation between ZBI-reported financial concerns and overall burden score in caregivers of children with chronic conditions [19].

Though these results are compelling, we identify several limitations. First, the sample size of patients who completed the questionnaires is small. However, in the context of ~3000 identified individuals with CCHS worldwide since 1970, our cohort is substantial. Also, the use of well-validated questionnaires strengthens the results, despite a relatively small cohort. The collection of data without identifiers was necessary due to regulatory restrictions. The study design and ultra-rare nature of this disorder precluded capture of clinical correlative data that could have increased risk of patent re-identification. The restricted clinical detail available limited interpretation of results and precluded connection of patient to caregiver responses. The complexity of the respondent's condition (mode of ventilation, severity of Hirschsprung, etc.) is unknown. Prior work has identified differences in perceived QoL in individuals with invasive versus noninvasive home ventilation [21]. This relationship should be considered in future CCHS research. Similarly, confirmation of the specific *PHOX2B* variant among participating individuals was not possible. A genotype-phenotype relationship is well-established in CCHS [10, 11], and the impact of genotype on QoL and caregiver burden requires further exploration. Next, our study did not include assessment of availability of home nursing, complicating interpretation of caregiver burden (or not). However, this availability generally varies by country, and our study did not

find any relationship between reported burden and country. Our study did not collect information that would allow comparison of QoL in those diagnosed in the newborn period as compared to someone with later-onset CCHS (diagnosed after 1 month of age, into childhood or adulthood), but this is an important consideration for future study.

In summary, this study demonstrated reduced QoL in individuals with CCHS and high levels of burden in caregivers of these individuals. Specific areas of concern for both patients and caregivers were identified. Results provide an initial step in understanding the impact of CCHS on patients and their caregivers, which should heighten awareness of their needs to optimize care and minimize burden. This research suggests value of a prospective study of QoL in CCHS including patients, caregivers, and other family members with an original survey designed and validated to more specifically address the CCHS experience. This work highlights the value of international collaboration amongst patient associations and investigators, working together to advance research in ultra rare disease. Future studies should include younger individuals with CCHS as well as those with later-onset CCHS (diagnosed in childhood or adulthood). More detailed clinical information should be collected to address type of respiratory support (e.g., tracheostomy vs. noninvasive ventilation), specific *PHOX2B* genotype, access to home nursing (or not) and specialized care centers, home technology (back-up ventilator, oximetry, capnography and its use), and common CCHS-associated morbidities (e.g., Hirschsprung Disease, tumors of neural crest origin, etc.). The overall goal is to identify healthcare, psychological and financial burdens and opportunities to reduce them. This will require partnership among patients, families, advocacy organizations, and healthcare providers with extensive experience in CCHS. Results will serve as a foundation for subsequent research to further advance our understanding of the burden of CCHS, clarifying targets for intervention to reduce morbidity and improve quality of life for patients and their caregivers.

Author Contributions

Casey M. Rand: formal analysis, writing – original draft, writing – review and editing, funding acquisition, visualization. **Julien Pelissou:** investigation, formal analysis, writing – original draft, writing – review and editing, data curation. **Narayanan Krishnamurthi:** formal analysis, writing – review and editing. **Xenia Proton de la Chapelle:** conceptualization, writing – review and editing, supervision, writing–original draft. **Martin Samuels:** conceptualization, writing – review and editing. **Melinda Riccitelli:** conceptualization, writing – original draft, writing – review and editing. **Linda Dokas:** conceptualization, writing – original draft, writing – review and editing. **Ajay Kasi:** writing – original draft, writing – review and editing. **Bruno Massenavette:** conceptualization. **Marie-Emilie Lampin:** conceptualization. **Claire Loire:** conceptualization. **Debra E. Weese-Mayer:** writing – original draft, writing – review and editing, funding acquisition.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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