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Research Article

Neurocognitive Function and Quality of Life with Congenital Central Hypoventilation Syndrome

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Abstract

Aim: To examine the cognitive development and health-related quality of life in patients with Congenital central hypoventilation syndrome (CCHS).

Methods: Eleven patients with CCHS in Sweden were contacted and all agreed to participate. The eight children (five female) and three adults (all female) were included at 6-31 years of age, having been diagnosed at up to four months of age. Most were non-invasively ventilated at night using face masks. Age appropriate Wechsler scales were used to measure general cognitive development, (IQ), and health-related quality of life with the KIDSCREEN-52 self- reported questionnaire.

Results: CCHS was confirmed by chromosomal analyses and the genotypes varied from 25 to 33. Four subjects had an average full-scale IQ, four a delayed full-scale IQ of 71-85 and two had an IQ of less than 70. The performance in the visual motor integration (VMI) test varied from extremely low to average. Six children were assessed for quality of life and most of the answers indicated an average or high level. The results were similar to other cohorts of CCHS patients.

Conclusions: Most participants reported a good quality of life including self-perception, although average to delayed scores were found in cognition and visual-motor coordination tests.

INTRODUCTION

Congenital central hypoventilation syndrome (CCHS) is a very rare disease that presents in the neonatal period. According to the National Board of Health and Welfare the incidence in Sweden was lower than one per 100,000 newborn infants and that 20 living patients were known in the country [1]. In France, the incidence has been estimated to be one per 200,000 live births [2].

The typical symptoms of CCHS are malfunctions of respiratory control and severe hypoventilation[3], mainly due to a deficient carbon dioxide drive. The patients are unable to breathe spontaneously during quiet sleep, but they seem to breathe better during wakefulness and active sleep. This means that patients with CCHS require mechanical ventilation while they sleep and sometimes they also need this ventilatory support when they are awake.

CCHS can lead to a number of other health issues and one important risk factor is cognitive deficits due to hypoventilation leading to hypoxia. There is also a risk for autonomic dysregulation including cardiac symptoms such as decreased heart rate variability during sleep, disturbed temperature control, decreased perception of pain and anxiety and neuropsychological symptoms [3]. CCHS is often associated with other disturbances of the autonomic nervous system affecting the iris, tear glands and intestines i.e. Hirschsprung disease. In addition, patients face an increased risk of being affected by neural crest tumors [3].

Carrying out a PHOX 2B polyalanine repeat expansion mutation (PARM) test is necessary as this gene defines CCHS [3]. It is also known that the PHOX2B mutation aids in predicting the respiratory compromise and in the ANS associated PARMs in exon 3 of PHOX2B gene produce genotypes of 20/24 to 20/33. Over 90% of CCHS cases are de novo and 20/25, 20/26 and 20/27 genotypes are the most commonly described. In less than 10% a non-polyalanine repeat expansion (NPARMs) is found in the end of exon 2 or in exon 3 of the PHOX2B gene.

This includes small insertion-deletions such as missense and nonsense or frameshift variants. Most of these mutations are de

novo and approximately 10-25% of asymptomatic parents are responsible for transmission to their offspring. In some families, the gene can also be inherited as an autosomal dominant trait to variable degrees. PHOX2B phenotype analysis supports a relationship between the number of polyalanine repeats or the NPARM mutation and clinical phenotype severity. Longer PARMs appeared to increase the risk for neurocognitive deficits [4]. It has been reported that preschool children with PHOX2B 20/25 essentially showed normal development, but that it was repressed in groups with the 20/26 and 20/27 genotypes [5].

There have been very few studies on cognitive development of children with CCHS and those reported have focused on very small groups of subjects, as would be expected with such a rare disease. These studies have shown that most children had impaired intellectual functioning with a wide group range of IQ from normal to well below normal [5-9]. In a study of a single seven years old girl with CCHS, a comprehensive neuropsychological test battery was used with a follow-up at 10 years of age. The results revealed a mixed composition of lowered IQ, deterioration of executive functions and social cognition, but improved ability in arithmetics and visuo-cognitive tasks [9]. Studies have also revealed impaired cognitive functions with regard to measurements of achievement, mental processing, receptive language and visual-motor integration. When mental and motor indices were measured using the Bayley scales for infant development, they were found to be below normal levels in preschool children, indicating that developmental delay was already present when children with CCHS were very young [5].

The aim of this study was to assess cognitive development and quality of life in a Swedish cohort of patients with CCHS.

METHODS

Participants

We were able to identify 20 Swedish patients with CCHS. Eleven of the 20 identified patients or their parents agreed to participate (Table 1). The age range of the children was broad, from 6 to 31 years. Three where less than one year of age, two adults were not able to recruit to clinical follow-up and one adult could not give informed concent due to intellectual disability. One was living abroad and two patient were lost to follow-up (Table 2).

The investigations took place at Astrid Lindgren Children's Hospital, Stockholm or the Children's University Hospital in Uppsala, or at the child clinic of the participant's home town. Demographic data were obtained from medical records and a structured (face-to-face) interview was carried out with the adults or the children's parents. The psychological screening process lasted about three-and-a-half hours and was carried out by one of the authors (KB) who is a licensed psychologist. The parents and/or the personal assistant could stay with the child if necessary. None of the participants were ventilated during the day, which means that the ventilator equipment did not interfere with the examinations.

Ethical approval was obtained from the local ethics committee of the Karolinska Institutet (EPN 2015/3:6), Stockholm, Sweden, and all participants signed the informed consent for the study.

Table 1: Clinical data of the included patients.

Patient	Gender	Karyotype	Age at test (years)	Kind of ventilation when tested	Comorbidity
1	M	28	16	Trach.	0
2	F	not known	10	Trach.	HD®
3	M	31	16	Mask	cardiac
4	F	26	6	Phren	dental
5	F	33	11	Mask	dental
6	F	27	12	Phren	0
7	F	25	9	Trach	0
8	F	33	31	Trach	HD®,ASD*
9	F	26	23	Phren	0
10	F	28	31	Mask	0
11	M	27	10	Phren	HD

HD®: Hirschprung´s disease; ASD*: Autistic Spectrum Disorder; Phren: Phrenic Pacer; Trach: Tracheostomized

Table 2: Patients not participating.

Gender	Phox2B	Reason
Male		Declined clinical visits
Female	25	Declined clinical visits
Female	Not able to sign informed consent, due to ID	
Girl		Living abroad
Boy		Lost to follow up
Boy		Lost to follow up
Boy	26	<1 yr at study
Girl	25	<1 yr at study
Boy	26	<1 yr at study

Psychological tests

A number of validated tests were used to measure cognition in a variety of domains, as well as different aspects of health-related quality of life (QoL).

General cognitive level was evaluated with an age-appropriate Wechsler Scale, i.e. the Weschler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) [10], an abbreviated form of the Weschler Intelligence Scale for Children-Fourth Edition (WISC-IV) [11,12], or the Weschler Adult Intelligence Scale, Fourth Edition (WAIS-IV) [13].

The results are presented as an IQ for the full scale and for each sub-index analysing verbal comprehension, perceptual resoning, working memory (not specified in WPPSI-III) and processing speed. All IQ have a mean of 100 and a standard deviation of 15.

The Beery-Buktenica Developmental Test of Visual-Motor Integration-Sixth Edition (Beery- VMI) [14], including copying, visual perception and motor coordination, was chosen to assess the participants ability to integrate visual and motor skills. Results are reported in standard scores with a mean of 100 and a standard deviation of 15.

Quality of Life (QoL) was assessed using the KIDSCREEN-52 [15], for children aged 8-18 years. KIDSCREEN-52 is a self-reported questionnaire that cover 10 dimensions of health-related QoL: physical wellbeing (physical activity, energy and fitness), psychological wellbeing (psychological wellbeing, positive emotions and satisfaction with life), moods and emotions (experiences of depressive moods, emotions and stressful feelings), self-perception (perception of self, including how the appearance of the body is viewed), autonomy (opportunity for the person to create social or leisure time), parental relationships and home life (relationship with the parents and the atmosphere at home), social support and peers (nature of the persons relationships with other children/adolescents), the school environment (perception of the persons cognitive capacity, learning and concentration, and feelings about school), social acceptance (aspects of feeling rejected by peers in school) and financial resources (perceived quality of financial resources). The answers range from zero to five, with a total for each dimension, with higher values indicating a more positive response. The raw scores are then converted into T-values (M=50, SD=10). According to KIDSCREEN-52 manual a T-value of 45-55 is considered to be a normal level of QoL, and higher values indicate a higher health related quality of life. Values below 45 are considered"noticeable".

RESULTS

Demographic data

The demographic data are presented in Table 1. The diagnosis of CCHS was usually suspected within a month of birth and confirmed by chromosomal analyses. The genotypes varied from 25 to 33, with one each of karyotypes 25 and 31 and two each of karyotypes 26, 27, 28, 33 and one NPARM. Most subjects suffered from cyanosis soon after birth. Eight children were mainly ventilated by mask, while three were tracheostomized. Six of the mask ventilated children received diaphragmatic pacer at an older age (4-8 years). One patient also required a cardiac pacemaker due to sinus pauses during teenage. Two children and one adult were diagnosed with Hirschprung disease (Table 1). Ten of the 11 patients required glasses, mainly due to refraction errors. Two patients had a squint and one had cerebral visual impairment. Six of the eight children had been admitted to a pediatric intensive care unit at some point, mainly due to pneumonia.

All children were supervised by personal assistants, including six parents, when they were connected to the ventilator at night. The youngest children also received support during the day at sleep. Six children attended a daycare center from 2-4 years of age and then continued to a mainstream school with extra learning assistance if required. Of the remaining two children, one child attended special classes for children with intellectual disabilities and the other a school form for children with a neuropsychiatric diagnosis. Two adults were employed, as a social worker and a nurse, and the third was studying.

Psychological data

The participants were tested at 6-31 years of age and the results are shown in Table 3. One participant, aged 6 years, was not able to complete the Wechsler test due to lack of endurance. The range of full scale IQ was broad, from extremely low to average (IQ 55-100) and the group median was noticeably lower (> 1SD) than that of the general normative population (Table 3). Working memory was found to be highest and relatively equal between females and males. Together with verbal comprehension it constitutes the strengths of cognition in the groups.

The results of the Visual motor integration test (VMI) (Table 4), show likewise a broad range of performance from extremely low to average. All but one participant needed glasses, mainly due to refraction errors, but the results from the VMI test did not show a specific delay in perceptual issues when compared with the cognitive levels according to the Wechsler scales. The FSIQ and the Beery copying tests have almost the same distribution for the two highest levels. Four out of the 10 FSIQ and four of the 11 copying results represent an average level, while four respective three results are delayed. Six of the 11 participants reached an average level of fine motor coordination.

The questionnaire regarding health-related QoL was designed for school children aged 8 to 18 years. Six out of eight children were able to participate. They all were satisfied with their lives (Table 5). Three reported a high level of psychological well-being and three said their well- being was average. They all had a positive self-perception, and almost all thought they were in a good mood with positive emotions. Two boys and one girl reported reduced physical health and activity. The school, peers and bullying dimensions were looked upon to be of an average or high quality.

DISCUSSION

Our main findings were that half the group of children suffered from moderate cognitive and visual-motor deficits. While the majority in our group had good working memory, their

Table 3: Median and range IQ-scores1 on the Wechsler scales for the whole group and divided into gender.

	All (n=11)		Female (n=8)		Male (n=3)	
	Mdn	*Range*	*Mdn*	*Range*	*Mdn*	*Range*
FSIQ	79.5	55-100	92.0	55-100	73.0	61-85
VCI	90.0	68-110	95.0	68-104	78.0	73-110
PRI	77.0	53-97	80.5	53-97	77.0	69-90
PSI	80.0	62-103	84.0	72-103	75.0	62-85
WMI	96.0	61-109	96.0	61-109	100.0	70-100

[1]General population: mean = 100, SD = 15

Table 4: Results on Beery VMI.

	VMI Integration		Visual Perception	Motor Coordination
Participant No.	Sex	Standard score1	Standard score1	Standard score1
1	M	60	96	76
2	F	88	96	72
3	M	81	93	86
4	F	70	61	90
5	F	94	95	86
6	F	77	81	105
7	F	96	117	112
8	F	< 45	45	86
9	F	83	97	81
10	F	87	81	81
11	M	57	81	59
Median		81	93	86
Range		45-96	45-117	59-112

1General population: mean = 100, SD = 15

Table 5: Quality of Life according to KID-SCREEN 52. (n=6).

T-scores 1	Median	Range
Physical wellbeing	46.15	39.0-54.4
Psychological wellbeing	54.8	47.9-61.5
Moods and emotions	57.15	41.2-61.6
Self perception	59.15	49.8-62.8
Autonomy	48.75	39.6-59.7
Parent relations and home life	53.5	43.8-61.6
Peers and social support	50.8	48.3-61.8
School environment	57.55	49.0-66.6
Social acceptance (bullying)	56.35	45.9-57.8
Financial resources	53.4	38.6-60.9

1 General population mean = 50, SD = 10

processing speed was marked reduced. The patients also tended to have a better verbal IQ than perceptual IQ, in accordance with previous studies [8,9].

Interestingly, we found that the QoL was usually described as good, although this could only be assessed among six of the eight children. All the children valued their psychological wellbeing, they reported that their relationships with their peers and their school experiences were average or even high and they had a confident self-perception. It was interesting to note that none of them felt bullied by other children. Physical well-being was the only dimension with low scores probably as a logical consequence of their medical condition.

A strength is that we could use a multiple of cognitive measurement and a self-answered health-related quality of life. The weakness of the study is that the results are based on a very small group of patients, but this is the situation for most studies on CCHS. All the published studies on the cognitive development of children with verified CCHS, show a broad range of IQ. These range from intellectual deficiency to well above average, with a mean value of about one standard deviation below normality.

It is known that neurocognitive exposedness starts very early in the CCHS process [5,6,9]. However, it is still not clear whether or not this neurocognitive impairment is related to the intrinsic CCHS genotype or the pathophysiological factors the children with CCHS are confronted with, or both. In our study, the female aged 9 years with genotype 25 had the best IQ results, with an FSIQ of 101 in the cognitive tests, which agreed with previous findings. However, another female aged 10 with genotype 33 was just as successful, with an FSIQ of 96. The number of patients in our study was limited, making it impossible to relate the results of the psychological tests to the various genotype. Other factors can affect IQ, including hypoxic events, other diseases and altered cerebral autoregulation. In fact, no specific cognitive profile has been connected to different genotypes [9].

In our study, the parents reported that the children demonstrated low levels of psychological distress and good coping responses, which disagree to some extent with a previous study [7], on nine Swiss children with a mean age of 7.5 ± 2.5 years (range 3-11). The parents had answered the Child Behavior Checklist questionnaire and reported that their children had problems with attention and social interaction. However, the cognitive tests showed a near to normal full-range IQ of 84.4 but a vast standard deviation of ± 23.2.

Zelko et al. [8], studied 20 children with PHOX2B-confirmed CCHS and reported that the group mean for general intellectual functioning was one standard deviation below the population mean. The method of ventilation for this study, which was published in 2010, was that the main form of ventilation required tracheostomy-ventilator support 24-hour, and diaphragm pacer ventilatory support during the day. Only three received nocturnal support.

Our study provides a clinical picture of CCHS in Sweden and was not carried out in order to answer the question of ventilatory management and neurocognitive outcome. Even if most of our patients were ventilated non-invasive, the number of patients was too small to draw any conclusions regarding ventilation management and neurocognitive outcome. Also none of our subjects needed ventilatory support during the day. When trying to answer the question of ventilatory management and neurocognitive outcome and controlling for genotype, there is a need to include many centers in Europe and the US to have enough statistical power.

In the group of non-included individuals three were infants and two adults were much older than the adults in the group of included participants. Furthermore, some of the participants were not able to recruite due to a lack of compliance to participate in any clinical visits at the hospital for several years. One participant was not able to sign informed consent due to intellectual disability. It is possible that these factors may have affected our results in either direction.

From a family network of CCHS with participants from US and Europe male-to-female ratio is known to be 1:1 [16]. This differs from our cohort and we have 73% female participants. This could be related to the small sample size. However, this is in accordance with a French [2], cohort with 60% females. An increased 2-year mortality was seen in male patients compared to female patients

in the French cohort. To the best of our knowledge no child within our CCHS patient group, born since year 2000, has died.

CONCLUSIONS

Most of the subjects had average to delayed scores in cognition and visual-motor coordination tests. Due to this it is important that children with CCHS undergo a neurocognitive assessment as a complement to the regular controls of ventilation, in order to identifty any cognitive impairments at an early stage and support the child for a suitable educational level. It is reassuring that those patients who were tested for QoL were found to have good psychological well-being and self-perception.

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