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CONGENITAL CENTRAL HYPOVENTILATION SYNDROME AND HIRSCHSPRUNG DISEASE: A RETROSPECTIVE REVIEW OF THE FRENCH NATIONAL REGISTRY CENTER ON 33 CASES.

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INTRODUCTION

Central congenital hypoventilation syndrome (CCHS), also known as Ondine's Curse, is a rare disease due to a defect in the proliferation and migration of neural crest cells, thus resulting in altered autonomic nervous system control of the respiratory system [1]. The diagnosis is suspected upon observation of neonatal respiratory distress requiring intubation and ventilation and in the absence of pulmonary, cardiac, or muscular abnormalities. The implication of PHOX-2B gene was discovered in 2003, with 90% of patients showing polyalanine repeat expansion (PARM), adding 4 to 13 alanines to the 20-residue polyalanines [2][3]. In 1978, Gabriel Haddad described for the first time the association between CCHS and Hirschsprung disease (HD) [4]. Since then, multiple case-reports of "Haddad's syndrome" were published and reviewed in 1998 by Croaker (46 cases) [5]. In 2005, Trochet [2] described a multicenter CCHS population including 46 cases of CCHS associated with HD. Those studies showed that 20% of CCHS cases were associated with HD, of which 20% were recto-sigmoid forms. Unlike isolated HD, which predominantly affects males, male to female ratio was 1:1 in CCHS associated HD. The major limitation of those studies was the absence of long-term follow-up.

In 1996, a national registry was created collecting all cases of CCHS in France. The principal aim of this study was to describe the characteristics and long-term follow up of the patients suffering from CCHS associated with HD enrolled in the registry. The secondary aim was to investigate the correlation between the severity of CCHS and the extent of HD.

PATIENTS AND METHODS

Database and study design

In 1996, a national registry center was created in Robert Debré Children University Hospital to collect all data from patients diagnosed with CCHS. Data was collected retrospectively for cases prior to 1996 and prospectively thereafter. A national ethics committee approved the registry and subsequent studies in 1996.

All patients born with both CCHS and HD (CCHS/HD) were reviewed. No cases were excluded.

For all patients, the medical records were reviewed. Data collected included date of birth, sex, date of death, cause of death, characteristics of CCHS and HD, genetic test results when there were available and follow-up regarding educational, respiratory, and digestive outcomes.

All patients suspected of having CCHS were transferred to the intensive care unit (ICU) at Robert Debré University Hospital. To confirm diagnosis of CCHS, each patient underwent polysomnography and genetic testing. Once the diagnosis was confirmed, patients returned to the initial medical center. All patients who showed early signs of respiratory distress required invasive ventilation. Those who did not either died within the first 2 months of life or were quickly weaned off invasive ventilation and switched to non-invasive ventilation during sleeping hours.

HD diagnosis was suspected upon observation of neonatal obstruction and confirmed by rectal biopsy.

A questionnaire regarding surgical follow-up, nutritional and intestinal functional outcomes was sent to all survivors.

To determine if a correlation existed between the severity of CCHS and the extent of HD, CCHS was categorized as severe or non-severe. We defined severe CCHS as requiring constant ventilation for more than a year or mortality unrelated to a digestive cause. Non-severe CCHS was defined as patients who

had successfully been weaned off from mechanical ventilation within the first year of life and requiring respiratory support only during naps and at night-time. Hirschsprung Disease (HD) cases were classified as either long-segment HD (aganglionosis extended to above the splenic flexure or total colonic form) or classic HD (left-colonic or recto-sigmoid forms). Patients for whom limited care strategy was decided (either for severe respiratory insufficiency where it was impossible to wean the patient off ventilatory support or very long or severe form of HD) were excluded from this analysis.

Statistics analysis

Data were analyzed using SAS statistic software (version 9.4, SAS Institute Inc., Cary, NC, USA). For descriptive analysis, data were expressed in median with ranges. Categorical variables were compared using either a Chi-squared test or a Fisher's test when appropriate. Survival data were estimated with Kaplan-Meier curves. Log-rank test was used to compare survival data curves. Two-tailed p values <0.05 were considered significant.

RESULTS

Among the 170 patients listed in the national registry, 33 (19.4%) showed the association CCHS/HD and were eligible for this study. Male-to-female ratio was 1:1 (15 boys, 18 girls). Patients were born between 1978 and 2016, including 8 patients born before 1996. They were initially treated in 17 different medical centers.

Prenatal Diagnosis

Gestational hypertension and diabetes were present in respectively 9% and 6% of our population.

Polyhydramnios was present in 9%.

CCHS characteristics

Diagnosis: Of the 33 patients, 32 (96%) showed early signs of CCHS. One patient presented with nocturnal desaturations associated with HD and was diagnosed with CCHS at the age of 6 months.

Treatment: Eighteen (54%) patients required a tracheotomy within a median time of 66 days [29-131 days]. Diurnal ventilation was stopped within 1 week in 7 patients, within 6 months in 5 patients, and within a year in 4 patients. Two patients still received invasive ventilation at the age of 1 year old.

A phrenic pacemaker was implanted in 2 patients with good outcomes on their respiratory autonomy.

HD Characteristics

Diagnosis: Twenty-three (70%) patients were diagnosed within 1 month of life, 7 (21%) patients within the first 6 months of life. Three (9%) patients, all born before 1995, had a delay in diagnosis due to unspecific symptoms or difficulties in interpreting the rectal biopsy results.

Extent of the aganglionic segment: classic HD forms represented 45% of the cases whereas long-segment forms represented 55% of the cases (Figure 1).

Treatment

A total of 8 patients (24%) were treated with daily irrigation. Within these, 4 patients were transitioned to limited care strategy and another 4 died of CCHS complications before surgery. Seven patients (21%) received a colostomy without undergoing a pull-through procedure. Two of these infants were transitioned to limited care strategy after colostomy creation and 5 died before surgery. Eighteen patients (55%) underwent a pull-through procedure, of which 8 had a colostomy prior to curative surgery. The median age at the time of the pull-through procedure was 113 days (7 days – 6 years). The surgical procedure was a trans-anal pull-through in 5 cases, a Duhamel procedure in 8 cases, and a Swenson or Soave procedure in 1 case each. For three patients, surgical technique was not available.

Overall treatment is summarized in Table 1.

Correlation between Severity of CCHS and Extent of HD

No correlation between the severity of CCHS and the length of the aganglionic segment was found ($p=0.13$) (table 2)

Genetic testing

The genetic results were available for 26 patients who were tested for PHOX-2B mutation. All patients tested had a PHOX-2B mutation, of which 21 had Polyalanine Repeat expansion (PARM). The most frequent expansion was 7 alanines ($n=13$). The remaining patients ($n=5$) had Non PARM or also called Polyalanine Repeat Mutation(frame shift mutation, missense mutation...). Only 2 patients presented with neuroblastoma. Statistical analysis was not performed due to the small sample size but no evident correlation between the length of the expansion and the extent of HD was observed (Figure 2).

Mortality or Morbidity

Overall mortality was 57%, with 70% of these infants that died within the first 6 months (Figure 3).

The mortality rate related to the surgery was 6% (2 patients died shortly after surgery, 1 of septic shock after colostomy creation and 1 after undergoing pull-through procedure). There were 6 other complications after pull-through procedures: ileus obstruction ($n=2$), fascial dehiscence and site infection ($n=1$), recurrent bowel obstruction ($n=1$), chronic constipation due to a transition zone pull-through requiring a redo surgery ($n=1$), anastomosis fistula that evolved into stricture and required several dilatation sessions under general anesthesia ($n=1$).

We found that mortality for long-segment HD was significantly greater than for classic HD ($p=0.005$) (Figure 4). Gender was not correlated with mortality, although statistical analysis was rendered impossible as conditions for Kaplan-Meier survival analysis were not met (Figure 5). Causes of death are shown in Table 3.

The mortality rate was 68% (15 out of 22 patients) during the 1st decade, mainly related to pulmonary complications and infection. The limited care strategy was concerning 3 patients. During the 2nd decade, the mortality rate was 36% (4 out of 11 patients), the limited care strategy being the most frequent cause of death (3 out of 4 patients).

Long-term outcome

Fourteen patients were still alive at last follow-up. Four were less than 3 years old, six were between 5 and 17 years, and all were going to school. Four patients were 18 years old or older: 2 were going to university, 1 was employed and 1 was unemployed.

Respiratory outcome: Twelve patients required nocturnal ventilation support, including 9 via a tracheostomy and 3 by non-invasive ventilation. One patient still required continuous invasive ventilation. The patient with a delayed diagnosis of CCHS had not required any ventilation support at last follow-up.

Digestive outcome: Out of the 14 patients still alive, 9 returned the questionnaire. Other 3 questionnaires were filled out according to the last medical report. Data were missing for two patients. All were regularly followed for their respiratory disease (at least once a year) but 91% declared no surgical follow up. All received feeds orally, with one patient requiring enteral supplementation through a gastrostomy. Regarding intestinal function, 16% complained of diarrhea, 33% of constipation and 58% had occasional or daily soiling.

DISCUSSION

Contribution of this study

CCHS is a rare disease and its association with HD has seldom been reported in the literature. With 33 cases, this is the largest series of this particular association. As previous articles have shown, our study is concordant with the results reported. However, our data failed to demonstrate a correlation between the extent of the HD and the severity of the respiratory disease. The number of patients excluded from the analysis for limited care strategy possibly influenced this result as all of them presented long-segment HD.

No prenatal pathology clearly predisposes to CCHS/HD. Gestational hypertension and diabetes were present in respectively 9% and 6% of our population, which is similar to reported rates in the general population (10% and 4%, respectively) (6). Polyhydramnios seems slightly more frequent (9% in our cohort vs 1% in the general population) (7).

CCHS characteristics in the CCHS/HD association are similar to those of isolated CCHS in terms of tracheostomy rates and time to weaning from diurnal ventilation (8,9).

Hirschsprung disease treatment is heterogeneous. In our cohort, HD was managed in seventeen different medical centers, with each of them following their own protocol. With a median of 113 days [7 days-6 years], the timing of pull-through procedures was similar to typical HD patients (10,11). Delayed diagnosis of HD diagnosis can explain the wide variability in timing of the pull-through procedure. Another reason for this wide range can be that once the neonatal obstruction is stabilized, the numerous other comorbidities of these patients overshadows and delays surgical management of HD.

All cases of delayed HD diagnosis occurred prior to 1995. To avoid delays in diagnosis of HD, our center has since then implemented a systematic rectal biopsy for all CCHS patients. Ultimately, we determined that a systematic rectal biopsy was not superior to standard clinical evaluation in detecting HD.

Mortality due to HD associated with CCHS was high (6%) compared to isolated HD series reporting an overall mortality of 1-2.5% (12,13). One explanation for the higher mortality rate may be that, given their overall condition (eg ICU stay, invasive ventilation...), recovering from surgical procedures can be more challenging for patients with CCHS/HD.

Overall mortality was statistically higher in our cohort of CCHS/HD compared to isolated CCHS reported in literature (57 vs 38%) (14) but the number of patients for whom limited care strategy was decided was high. Unlike previous findings in isolated CCHS, we did not find an increased mortality in the first two years of life in boys (8).

All patient tested had PHOX-2B mutation, among which 80% were Polyalanine Repeat Expansion. Expansion of 7 alanines was the most represented mutation in the CCHS/HD association, unlike isolated CCHS whose most frequent mutations were expansion of 5, 6 and 7 alanines. Trochet et al. found similar results, whereas the American Thoracic Society found Non PARM as the most frequent mutation (2,9). Non PARM was confirmed in the only patient with total aganglionosis genetically tested, and another patient considered in this study as a right colonic HD for which a total aganglionosis was suspected even after her death. This could be regarded as a particular phenotype. Occurrence of neuroblastoma in association with congenital central hypoventilation and Hirschsprung's disease suggests that genes, involved in the development of neural-crest-derived cells, may be altered in these conditions. A constitutional R100L PHOX2B mutation was identified in three patients affected with tumours (15). Surprisingly, only 2 patients presented with neuroblastoma in our cohort.

This study is the first to evaluate long-term outcomes of patients with CCHS/HD. Results are promising, as mortality is low for children who survive beyond 1 year old. Almost all patients were weaned off nocturnal ventilation and were at their expected education level. Surgical follow-up is however lacking as almost all patients report having no follow-up at all. Yet, 81% complained of either soiling, constipation or diarrhea with no more than oral treatments to control these invalidating symptoms. However, effective solutions exist as some studies report the potential of enemas to improve fecal incontinence in children with HD or anorectal abnormalities (16,17). Bowel dysfunction in HD should not be regarded as a fatality and affected patients would certainly benefit from a better management of their bowel movements by means of an optimized surgical follow-up.

Limitation of this study

There are several limitations to our study. Although most data were collected prospectively, this national registry center mainly focuses on CCHS, and some data on HD were occasionally missing and required a supplementary retrospective chart review.

It is also possible that medical centers omitted to include some patients to the national registry center. Moreover, it is possible that patients who were initially referred to the center for CCHS were later diagnosed with HD, without the medical record being updated.

Although this study reports a national study and is the largest of its kind, we were still only able to identify 33 cases. The small size of the sample renders extrapolation uncertain.

CONCLUSION

This study is the largest cohort study focusing on children born with CCHS associated with HD and their long-term outcomes. We show that mortality is higher in CCHS/HD than in isolated CCHS. We could not

find any correlation between the severity of CCHS and the extent of HD. Surgical follow-up of those patients is insufficient and implementing a dedicated multidisciplinary follow-up should be considered.

Figure 1: Distribution of aganglionic segment in Hirschsprung disease

Figure 2: Distribution of PHOX-2B mutations according to the extent of Hirschsprung disease.
 NPARM= Non polyalanines repeat mutation

Figure 4: Kaplan-Meier survival curves for short and long Hirschsprung disease

Figure 5: Kaplan-Meier survival curves for male and female patients

Table 1: Management of Hirschsprung's disease

			N (%)	Stoma (N)	Procedure (N)	
Incomplete Surgical management			15 (45)			
	Rectal Irrigation		8 (24)			
		<i>Recto-sigmoid</i>	0			
		<i>Left Colon</i>	1			
		<i>Right Colon</i>	6		none	
		<i>Small Bowel</i>	1			
	Stoma		7 (21)			
		<i>Recto-sigmoid</i>	0			
		<i>Left Colon</i>	0			
		<i>Right Colon</i>	5		none	
		<i>Small Bowel</i>	2			
Complete Surgical Management			17 (55)			
	Recto-sigmoid		7	yes (1) No (6)	TAPT (3) Duhamel (2) Swenson (1) Unknown (1)	
		Left Colon		7	yes (4) no (3)	Duhamel (3) TAPT (2) Soave (1) Unknown (1)
			Right Colon/SB		3	yes (3)

TAPT: Transanal Pull-through- SB:Small Bowel

Table 2: Comparison of HD and CCHS severity

	Short HD	Long HD	p
CCHS	15	18	
Non severe CCHS	11	5	0,13
Severe CCHS	4	7	
N/A (Limiting Care Strategy)	0	6	

Table 3: Cause of death

	N=19	%
Limited Care Strategy	7	37
CCHS Complications	8	42
<i>Pulmonary infection</i>	2	
<i>Sudden Death/nocturnal decanulation</i>	4	
<i>Status epilepticus (neonatal brain anoxia and damage)</i>	2	
HD Complications	2	10,5
<i>Septic Shock</i>	2	
Unclear	2	10,5
<i>Brain Stem Dysfunction</i>	1	
<i>Hypovolemic shock</i>	1	