

Congenital central hypoventilation syndrome and Hirschsprung's disease

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Abstract

Five cases of the Hirschsprung's disease-congenital central hypoventilation syndrome (CCHS) association are presented and 41 other published cases reviewed. These children have a distinct pattern of associated features, an equal sex incidence, and a characteristic spectrum of disease severity which suggests that the condition is genetically distinct from other cases of Hirschsprung's disease. While approximately 1.5% of Hirschsprung's disease patients, and 10% of those with total colonic aganglionosis, will have CCHS, up to 50% of CCHS patients will have Hirschsprung's disease. Approximately 20% of CCHS/Hirschsprung patients will also have neuroblastoma or ganglioneuroma, usually multiple. Abnormalities of the eye and autonomic nervous system are also common. The ventilatory abnormality is usually evident on the first day of life. The aganglionosis is also severe, with more than half (59%) of the patients having aganglionosis extending into the small bowel.

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Keywords: Hirschsprung's disease; congenital central hypoventilation syndrome; total colonic aganglionosis; neurocristopathy

Hirschsprung's disease is a condition caused by congenital absence of ganglion cells from the enteric nervous system, resulting in bowel obstruction ranging in severity from chronic severe constipation to complete obstruction and early neonatal death. It is thought to originate in a failure of migration of neural crest derived precursor cells,¹ although this is controversial and a hostile gut microenvironment may also contribute. Congenital central hypoventilation syndrome (CCHS) results in hypoventilation, most pronounced during sleep, with relative insensitivity to hypercarbia and a lesser insensitivity to hypoxia, in the absence of other abnormalities of the cardio-respiratory system. CCHS is also known as Ondine's curse, after a figure from Germanic mythology. Ondine's curse properly refers only to the condition where hypoventilation is restricted to the sleeping state. CCHS and Hirschsprung's disease were first reported together by Haddad *et al* in 1978.² Both are uncommon, and their co-occurrence suggests a common aetiology, probably involving a fault of neural crest development.

We here report the largest single series (five cases) of the congenital central hypoventilation

syndrome-Hirschsprung's disease association ("Haddad syndrome"). These children have presented to the children's hospitals of New South Wales and the Australian Capital Territory over the past 21 years, adding to the 41 already reported in English language journals. These children present a challenging spectrum of problems and represent a subgroup of more severely affected children with Hirschsprung's disease.

Methods

We identified cases by a retrospective review of Hirschsprung's disease admissions to children's hospitals in New South Wales and the Australian Capital Territory over the 21 year period from 1 January 1975 to 1 January 1996. During this period there were 341 admissions with this diagnosis to the three teaching hospitals. Patients who had the concomitant diagnosis of CCHS were then reviewed separately. At the time of writing two children are known to have died. The families of surviving children were contacted for follow up interview and the collection of blood for genetic studies.

We also reviewed published reports. Forty one previously reported cases of the association are summarised in table 1. An additional 10 patients have been reported without supporting detail^{25 26}; these are not included in the analysis.

Results

Clinical details of our five patients are summarised in tables 2 and 3. All had biopsy proved Hirschsprung's disease, and evidence of congenital central hypoventilation on monitoring in the intensive care unit or with formal sleep studies. There are two males and three females. Treatment was withdrawn from two, and there are three survivors. These children are now satisfactorily managed on home ventilation.

Three children had sigmoid aganglionosis and two had total colonic aganglionosis. In three patients this was confirmed on histology, and in two patients (one from each group) in whom the parents refused necropsy it was inferred from barium studies and rectal biopsy. Although barium enema is known to be misleading in as many as 30% of cases,²⁷ the presence of numerous nerve twigs in the rectal suction biopsy suggests less than total colonic aganglionosis.

Two of our cases had gastro-oesophageal reflux, one had dyscoordinated swallowing on barium swallow, and one had a complete absence of swallowing reflexes. Information on the fifth case is inconclusive.

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Table 1 Summary of clinical details of 41 cases of Hirschsprung's disease—congenital hypoventilation syndrome association

Author	Sex	Gest age	HSCR diagn	Age vent	Length affected	Eye/ear/neurological/ autonomic	Neuroblastoma/other	Family history	Outcome	Ref
Haddad	F	37 wk	7 d	Hours	DC +	?	No	Sib	Died 2 months	2
Haddad	F	37 wk	5 d	3 h	TCA	Hypotonia; fits; GOR*	No	Sib	Died 5 months	2
Haddad	F	Term	10 d +	Minutes	Ileal	Hypotonia; fits	Ganglioneuroblastoma†	No	Died 2 months	2
Bower	M	Term	3 d	Day 2	Sigmoid or less	Episodes diaphoresis	Neuroblastoma	?	Died 9 months	41
Stern	M	Term	3 d	Day 1	Ileal	No	No	No	Died 15 months	42
Guilleminault	M	Term	4 d	4 d	TCA	Hypotonia	No	?	Died 24 days	6
Guilleminault	M	Term	2 d	2 d	TCA	Fits	No	No	Alive at 24 months	6
Pettersson	M	?	?	?	TCA	?	No	?	Died 4 weeks	7
O'Dell	M	Term	21 d	Birth	Ileal	?	No	?	Alive 5 months	8
Poceta	F	Term	14 d	<1 h	PJ††	Ocular; BAER; hypotonia; fits	?	?	Died 40 days	9
Poceta	M	Term	2 d	Birth	TCA	Hypotonia; fits	?	?	Died 30 months	9
Sato	M	?	?	?	Trans colon	No	No	?	Alive 8 months	10
Roshkow	M	Term	?	?	MJ	No	No	No	Died 3 months	11
Roshkow	M	34 wk	?	?	Ileal	No	No	Stillborn sibs	Alive at 13 months	11
Roshkow	M	Term	?	?	PJ	No	No	?	Died 15 days	11
Weese-Mayer	?	?	?	?	TCA?	?	?	?	?	12
Weese-Mayer	?	?	?	?	TCA?	?	?	?	?	12
Levard	F	?	?	?	Trans colon	?	Ganglioneublastoma	?	?	13
Levard	M	?	?	?	TCA	?	Ganglioneublastoma	?	?	13
Hamilton	F	Term	7 d	6 h	Rectum	Esotropia	?	Half sib	Alive 54 months	3
Hamilton	M	Term	4 d	Birth	Rectum	?	No	Half sib	Alive 30 months	3
Minutillo	F	39 wk	3 d	8 h	Ileal	Ocular	Facial dysmorphism	No	Died 19 days	14
Gaisie	M	Term	5 d	Birth	?	?	Neuroblastoma	?	Died 7 months	15
Fodstad	F	Term	3 mo	20 mo	Rectum	No	No	No	Alive	16
Fodstad	F	?	1 mo	Birth	RS	Hypotonia, fits	No	No	Alive	16
Fodstad	M	36 wk	3 d	Day 1	Duodenum	No	No	No	Died 1 month	16
Mukhopadhyay	F	35 wk	Days	Birth	?	A-V malformation‡‡; hypotonia; fits	No	?	Alive at 36 months	17
El-Halaby	F	Term	13 d	Hours	Ileal +22cms	Ocular; mild hypotonia; fits	No	No	Alive at 57 months	18
El-Halaby	F	Term	16 d	11 h	R-S junction	Ocular; mild hypotonia	?	No	Alive at 17 months	18
El-Halaby	F	Term	20 d	4 h	SF	Ocular	ASD	No	Alive at 7 months	18
Verloes	F	38 wk	?	15 h	Trans colon	Fits**	Facial dysmorphism	No	Alive 2 years	19
Verloes	M	Term	4 d	4 d	TCA	GOR	No	No	Died 5.5 years	19
Stovroff	F	Term	1 d	Birth	Ileum	Ocular	Neuroblastoma	?	Died 2 months	20
Nakahara	M	37 wk	19 d	2 h	Trans colon	?	No	?	Alive at 13 months	21
Commare	M	Term	?	Birth	?	BAER; motility‡	?	?	?	22
Commare	F	Term	?	Birth	?	BAER; multiple§	Neuroblastoma	?	?	22
Commare	M	Term	Days	4 d	?	BAER; multiple¶	?	?	?	22
Commare	F	Term	?	18 h	?	Ocular; motility	?	?	?	22
Barber & Scobie	M	37 wk	>3 d	4 h	> TCA	Fits	No	No	Alive at 7.5 years	23
Barber & Scobie	F	Term	18 d	?	Sigmoid	No	No	No	Alive at 16 months	23
Kincaid	?	41 wk	2 mo	Day 1	TCA	?	No	?	?	24
Croaker	f	Term	3 d	Birth	Sigmoid	Heart rate; GOR	Scalp xanthoma	No	Alive at 47 mo	
Croaker	f	Term	3 d	12 h	TCA	Ocular; convulsions; GOR	No	No	Alive at 61 mo	
Croaker	M	Term	36 h	3 h	Sigmoid	Ocular; heart rate; GOR	No	No	Alive at 19 mo	
Croaker	F	35 wk	5 d	Birth	TCA?	Ocular; heart rate; absent swallow	Multiple perirenal masses.§§	No	Died 10 days	
Croaker	M	Term	36 h	30 min	Sigmoid?	BAER; heart rate; fits	No	No	Died 19 days	

*Also had abnormal oesophageal motility, and gastro-oesophageal reflux on barium swallow, and lack of heart rate variability.

†Also had idiopathic septal hypertrophy and subaortic stenosis.

‡Oesophageal dyskinesia and achalasia.

§Ocular abnormalities; heart rate changes; megaesophagus; excessive perspiration.

¶Cardiovascular instability; oesophageal dyskinesia and gastro-oesophageal reflux.

|| Oesophageal dyskinesia and gastro-oesophageal reflux.

**Also had recurrent hypoglycaemic episodes.

††Abnormalities of myenteric plexus even in proximal jejunum; abnormal peristalsis noted throughout gut.

‡‡Arteriovenous malformation involving both lobes of cerebellum, raises the question whether this child has true primary CCHS.

§§Including dysmorphic facies. ASD = atrial septal defect; BAER = (abnormal) brain stem auditory evoked response; DC = descending colon; GOR = gastro-oesophageal reflux; PJ = proximal jejunum; SF = splenic flexure; TCA = total colonic aganglionosis.

Summary (for those whose details are known)—sex: 51.2% male; gestation: 90% term (37 weeks or more); length: 60% total colonic aganglionosis or longer; mortality: 51.4% alive at time of reporting; neural crest tumour: 7 (+ 1 possible) reported: 7/43 = 16.3%

In this series there was no definitive evidence of neural crest tumour, although one case had undiagnosed retroperitoneal masses at the time of death. Features of autonomic dysfunction are common in other reports, and have been noted in table 1. An abnormal facies was noted in one case. The two surviving females have both had karyotype examinations, which are normal female to the 450

and 500 band stages of resolution, respectively. The surviving male is overseas and therefore unavailable for study at the time of writing.

Discussion

Congenital central hypoventilation syndrome results in a decrease in the depth rather than the rate of breathing, most severe during quiet

Table 2 Clinical features of CCHS/Hirschsprung patients

	Patient				
	1	2	3	4	5
Sex	M	F	F	M	F
Gestation (weeks)	39	39	35	>40	40
Birth weight (kg)	3.38	3.44	2.76	3.5	3.085
Length of aganglionosis	Sigmoid?	TCA	TCA?	Sigmoid	Sigmoid
Age at presentation of HSCR	Day 2	Day 3	Day 5	Day 2	Day 3
Age ventilated	30 minutes	12 hours	Birth	3 hours	Birth
Respiratory responses	No response to raised CO ₂	No response to asphyxia or CO ₂ 110 mm Hg when asleep	Raised CO ₂ , no polygraphy performed	Rapid O ₂ desaturation when asleep	No response to CO ₂ 50 mm Hg, and decreased O ₂ in quiet sleep
Alive	No	Yes: on home ventilation	No	Yes: on home ventilation	Yes: on home ventilation

CCHS = congenital hypoventilation syndrome; HSCR = Hirschsprung's disease.

sleep and less marked in rapid eye movement sleep. There is, however, a spectrum of severity, so that the more severely affected patients hypoventilate when both asleep and awake, and rate may also be affected. Insensitivity to hypercapnia is the most constant finding, with a variable response to hypoxaemia.²⁸

A recent report suggested that up to 30% of patients with Hirschsprung's disease may have some form of dysautonomia (Staiano A, *et al*: Autonomic dysfunction in children with Hirschsprung's disease. Abstract from 29th Annual Meeting of European Society for Gastroenterology and Nutrition, Munich, 5–8 June 1996). If this observation is true, then the CCHS/Hirschsprung combination may well represent the severe end of the spectrum for autonomic manifestations as well as for length of aganglionosis.

SEX RATIO AND LENGTH OF AGANGLIONOSIS

Of the 46 reported cases (including our own five), 21 were female and the sex of three was not stated. This 1:1 ratio is consistent with previous observations that the sex ratio in Hirschsprung's disease, which normally has a 4:1 male preponderance, approaches unity as the length of the involved segment increases.²⁹ The length of aganglionosis was definitely known for 34 of these cases, with another six doubtful and six unknown. There was no definite evidence that females were affected more or less severely than males; however, equal

numbers of males and females (eight each) had aganglionosis affecting the whole colon or ileum. The four most severely affected patients—with aganglionosis extending into the mid-small bowel or more proximally—were all boys. Counting three whose sex was unknown, 24 of the 40 in whom the information was available (60%) had aganglionosis that probably ($n = 3$) or certainly ($n = 21$) affected at least the whole colon.

Of those with less than total colonic aganglionosis, five of 16 had long segment Hirschsprung's disease with aganglionosis to the splenic flexure or beyond. Only eight had aganglionosis of sigmoid length or less, a striking reversal of the usual length distribution in Hirschsprung's disease (fig 1; table 4). Although the length distribution remains bimodal, the major peak of the distribution in CCHS/Hirschsprung patients is at the level of the ileocaecal valve, and there is a gradual tapering of the distribution into the proximal bowel. The difference of the distribution in CCHS/Hirschsprung patients compared with both the Down's syndrome/Hirschsprung combination and non-syndromic Hirschsprung's disease suggests a different aetiological mechanism for the former. The bimodal distribution implies that migrating ganglion cells may have to cross potential barriers at the level of ileocaecal valve and rectosigmoid junction, which become impassable in the disease state. Alternatively, it might suggest that the bowel is

Table 3 Associated features in CCHS/Hirschsprung patients

	Patient				
	1	2	3	4	5
Ocular	—	Pupil dilatation; ptosis	Pupil dilatation	Left amblyopia; unequal pupils; right Marcus-Gunn jaw winking sign	Normal
Brain stem auditory evoked response	Abnormal	—	—	Conductive hearing loss only	Normal
Heart rate	Decreased variability	Normal	Decreased variability pre- and postpartum	Asymptomatic bradycardias	Bradycardic episodes ("central dysrhythmia")
Swallowing	—	Gastro-oesophageal reflux	Absent	Gastro-oesophageal reflux, Dyscoordinated swallowing and aspiration	Possible gastro-oesophageal reflux
Epilepsy	Present	Present	—	—	—
Neural crest tumour	—	—	Infrarenal masses	Borderline high catecholamines. No mass found	—
Other	—	—	Facial dysmorphism; delayed myelination on brain MRI	—	Occipital scalp xanthoma
Family history	Not available	Mother: fits till age 10 Maternal aunt: hypothyroid Father: piebald	Maternal aunt with cyanotic congenital heart disease	Full history not available but, no history of CCHS	Maternal family history of benign goitre; no other CCHS/HSCR

CCHS = congenital hypoventilation syndrome; HSCR = Hirschsprung's disease; MRI = magnetic resonance imaging.

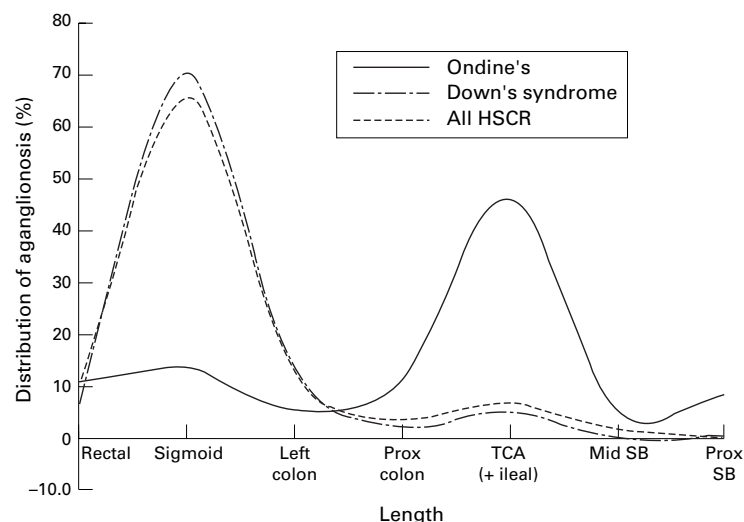


Figure 1 Distribution of aganglionosis in cases of Hirschsprung's disease (HSCR). SB=small bowel; TCA=total colonic aganglionosis.

populated by a small number of discrete clones and their progeny: if one clone is missing, sigmoid aganglionosis results; if several are missing, total colonic aganglionosis occurs (Cass DT: Abstract from First International Workshop on Hirschsprung's Disease, Genoa, Italy, March 1994).

Recent work has shown that the penetrance of mutations in the Hirschsprung's disease associated genes RET and the endothelin B receptor (ENDRB) is affected by sex.^{30,31} The equal sex incidence in CCHS/Hirschsprung patients suggests that a different mechanism may be at work in this condition. The very high incidence of associated autonomic anomalies supports this possibility by suggesting that the underlying anomaly may operate at an earlier stage of development than RET or ENDRB mutations, or over a longer segment of neural crest.

PATTERNS OF HYPOVENTILATION

While there are few data on normal respiratory values in infancy,³² of the patients with CCHS alone at our institution, two on home ventilation both presented late—one at 12 months, and one at 6 years (Seton C, personal communication). A third patient (who has since died) presented at the age of 3 years. In clear contrast to this, 90% of the cases in this collected series of CCHS/Hirschsprung patients were ventilated on day 1 of life: the median age for start-

ing ventilation in the 25 patients for whom the data are available was 3 hours. Khalifa *et al* asserted in 1988 that most cases of primary central hypoventilation occur in adult life, and that CCHS may represent a more severe form of this disease.³³ A recent paper noted that there was an excess of sudden infant death syndrome (SIDS) in relatives of patients with CCHS.²³ If SIDS is part of the same disease spectrum as CCHS, then clearly the CCHS/Hirschsprung combination represents another variant, as it is also at the more severe end of the Hirschsprung's disease spectrum.

ASSOCIATED FEATURES

Eyes

Overall 10 of the 46 patients reviewed here (21.7%) were noted to have abnormalities of the pupils, extraocular muscles, or eyelids, either unilaterally or bilaterally. In a series of 32 patients with CCHS (with or without Hirschsprung's disease) reviewed by Weese-Mayer *et al*, as many as 60% were said to have ophthalmic abnormalities.²⁸ Three of the five patients newly reported here have ophthalmic abnormalities, consistent with Weese-Mayer's report; this suggests that the low incidence in the collected series probably represents underreporting rather than a true difference in incidence.

Swallowing

An abnormality of swallowing or oesophageal motility was identified in four of our five patients. This suggests a generalised abnormality of gastrointestinal motility. This tendency is confirmed in the broader series, where overall 10 of 46 had evidence of oesophageal dysmotility, with or without documented reflux.

Hearing

Abnormal brain stem auditory evoked responses were identified in five of the 46 patients. It is not possible to say what percentage of CCHS/Hirschsprung children have a sensorineural hearing deficit as it is uncertain how often this was tested for. However, sensorineural deafness forms part of the Shah-Waardenburg syndrome, now known to be related to a defect in the endothelin signalling pathway.³⁴ Two of three children with near total intestinal aganglionosis but without CCHS who had brain stem auditory evoked response testing showed abnormalities consistent with inner ear dysfunction.³⁵ These results suggest that hearing loss in children with very long segment aganglionosis is likely to be more common than previously believed and should be tested for.

Neuroblastoma

There have been several previous reports of the association of CCHS and Hirschsprung's disease with neuroblastoma, and neuroblastoma with either of these conditions on its own.³⁶⁻³⁸

Of the 46 cases reviewed here, there were seven (15.2%) with confirmed neuroblastoma or ganglioneuroma. Our patient with perirenal masses on ultrasound would make an eighth. Thus 17.4% of the total group have sympathetic chain tumours. These tumours tend to

Table 4 Length of aganglionosis. Comparing lengths of aganglionosis between collected CCHS/Hirschsprung cases, and the Sydney 30 year experience of Hirschsprung's disease alone, or with Down's syndrome

Length	CCHS/HSCR (n)	CCHS/HSCR (%)	Down's syndrome/HSCR (%)	All HSCR (non-CCHS, non-Down's) (%)
Rectal	4	10.2	7.5	10.9
Sigmoid	6	15.4	70.0	65.2
Left colon	2	5.1	12.5	12.2
Rest of colon	4	10.2	2.5	3.6
TCA (+ ileal)	18	46.2	5.0	6.5
Mid-small bowel	2	5.1	0	1.5
Proximal small bowel	3	7.7	0	0
Total	39	100		

CCHS = congenital hypoventilation syndrome; HSCR = Hirschsprung's disease; TCA = total colonic aganglionosis.

be multiple and bilateral when present. There is no evidence that they were more common in the children with longer segment disease in this series. Three further patients with Haddad syndrome were reported to have raised catecholamines on at least one occasion, but without other evidence of neuroblastoma.²² Unfortunately, the falling rate of necropsy examinations makes it hard to be accurate in estimating the real incidence of neuroblastoma and related tumours in these children. Neuroblastoma should, however, be looked for in all children with the Haddad syndrome. This significant association suggests that adrenal tissue from these children is worthy of further study.

Other conditions

Various other conditions reported in association with this syndrome are listed in table 1. Three patients had facial dysmorphism, but so far there is no characteristic facial feature that will identify these children. Hypotonia and fits have often been reported (in 13 of the 46 patients); although these may be secondary to hypoxia, they could also represent a primary phenomenon. The mother of one of our patients who required antiepileptic treatment for several years also has a history of seizure disorder, pointing to the possibility of an inherited tendency.

INCIDENCE

The five cases we report here were identified by retrospective review of cases of Hirschsprung's disease presenting to New South Wales and the Australian Capital Territory teaching hospitals over 21 years. The total number of cases of Hirschsprung's disease presenting to these hospitals in the same period was 341. On this basis, the CCHS/Hirschsprung combination accounts for 1.5% of all Hirschsprung's disease cases. Uncomplicated CCHS presents to our sleep unit at a rate of much less than one case a year, and there are only two patients currently on long term home ventilation in the study area for pure CCHS without Hirschsprung's disease. A third patient has recently died (Seton C, Rosier M; personal communication). Currently there are three living CCHS/Hirschsprung patients from this series. CCHS/Hirschsprung's disease therefore comprises 50% of our CCHS population at most. In a survey of 32 CCHS patients in 1992, Weese Mayer *et al* found five patients (16%) with associated Hirschsprung's disease.²⁸ In a subsequent paper the same investigators stated that there are fewer than 100 published cases of CCHS (Weese-Mayer DE, Silvestri JM, Kenny AS, *et al*: Characterisation of CCHS. Paper presented at the Second International Hirschsprung disease meeting, Cleveland, Ohio, October 1995). The fact that our review now extends the number of cases of the CCHS/Hirschsprung association to 46 suggests that the risk of Hirschsprung's disease for CCHS patients may be higher than 16% (although it is possible that the CCHS/Hirschsprung syndrome may be relatively overreported compared with CCHS alone). El-Halaby and Coran found that three of their seven CCHS

patients on home ventilation (43%) had coexistent Hirschsprung's disease,¹⁸ a figure that broadly agrees with our own figure of 50%.

GENETICS

A family history was recorded in only three of our patients, and in none of these was there a family history of Hirschsprung's disease or CCHS. The family history is unknown or not stated in 21 of the previous 41 cases, but there are two sibling pairs in the 18 previous families for whom a family history is known, suggesting that the recurrence risk is similar to the recurrence risk for total colonic Hirschsprung's disease (approximately 10%). Of our three families for which we do have a family history, two have a history of thyroid disease, and one of pigmentary anomalies. These features may both be linked to separate specific Hirschsprung's disease related genes.³⁴⁻³⁹

A familial occurrence has been reported for both Hirschsprung's disease and CCHS separately. Complex segregation analysis suggests that the inheritance of CCHS is the same with or without Hirschsprung's disease, although this is based on only one positive sibship out of 50 CCHS probands.²⁵

It is of interest that Haddad syndrome has been transmitted as an apparently autosomal dominant characteristic to two half sisters with a common father.³ However, no defects in any of the known Hirschsprung's disease related genes have yet been reported in the CCHS/Hirschsprung association. Screening of the RET proto-oncogene has failed to show any mutation in Hirschsprung's disease or CCHS patients,⁴ and only one case report of a point mutation in the endothelin 3 gene in a case of pure CCHS has been published.⁵ Involvement of the endothelin signalling pathway may account for the frequent observation of abnormal brain stem auditory evoked potentials in these children, as mutations in endothelin 3 and the endothelin B receptor (ENDRB) are known to be associated with sensorineural deafness and Hirschsprung's disease. Interestingly, a point mutation in this gene in the Mennonite kindred is associated with a shorter segment form of Hirschsprung's disease, deafness, and pigmentary anomalies, unlike the long segment disease seen in CCHS/Hirschsprung patients.³⁰ Edery *et al* have reported a case of total colonic aganglionosis associated with deafness and depigmentation in an inbred family carrying an endothelin 3 mutation.⁴⁰ If the endothelin pathway is involved in this condition, it seems likely that modifiers also exist. If EDNRB and RET are not involved, then the RET ligand, glial derived neurotrophic factor (GDNF), remains a candidate gene. We have screened two of our five patients for GDNF mutations, but have found no evidence of mutations in this gene in these patients.

TREATMENT

The combination of a condition requiring long term ventilation with long segment Hirschsprung's disease, and its attendant problems, is a daunting one; however, three of our five patients remain alive and in good health at the

time of most recent follow up. The two children who died in our series did so after a considered withdrawal of treatment.

There have been 19 deaths from among the 41 patients in this series in whom the outcome is known. Six of those who died have been reported since 1990. They have a mean survival of 19 months. Those reported before 1990 (13 cases) died at an average age of 5.9 months. It is not surprising that improvements in total parenteral nutrition and home ventilatory support should be reflected in improved survival, and the improvement parallels the better prognosis of other children with total colonic aganglionosis over the last 20 years. Anecdotal reports (cited by Weese-Mayer at the International Hirschsprung's disease meeting in Cleveland in 1995) suggest that the first survivors of CCHS are now reaching adulthood, and that they have the potential for a healthy and largely normal existence, at least into their twenties.

Because of the well recognised link between total colonic aganglionosis and CCHS we suggest that all children with the former should undergo sleep monitoring after diagnosis, to rule out milder or less obvious forms of CCHS. It is possible that routine monitoring of other Hirschsprung's disease patients would pick up subtle and previously unrecognised ventilatory changes. In fact two of 19 children with total colonic aganglionosis treated in New South Wales since 1 January 1975 have clinical CCHS. Thus CCHS must be regarded as a significant risk in children with total colonic aganglionosis. Similarly, clinicians who make the diagnosis of CCHS should be aware that Hirschsprung's disease is common in these children, and a rectal suction biopsy should be considered if there is any concern about gut function. Finally, because of the high incidence of associated conditions, these children should be carefully assessed by their attending surgeon and physician, with particular care to exclude neural crest tumours and sensorineural deafness.

SUMMARY

The combination of CCHS and Hirschsprung's disease is a condition distinct from classical Hirschsprung's disease, and of greater severity. It occurs in approximately 1.5% of all cases of Hirschsprung's disease, and in 10% of cases of total colonic aganglionosis. The CCHS/Hirschsprung combination contributes up to half the case load of CCHS referred to respiratory units for home ventilation. Infants presenting to neonatal units with either total colonic aganglionosis or CCHS alone should be screened for the other condition. Of all the children reviewed, approximately half are dead, half are female, and half have total colonic Hirschsprung's disease.

There is a high risk of associated neuroblastoma, which may occur in nearly 20% of cases. This should be looked for whenever the CCHS/Hirschsprung combination is seen. Other associated problems are common; while these may be less severe they are clinically important, and include sensorineural deafness,

ocular problems, and disturbances of gastrointestinal motility.

Management is difficult, and a multidisciplinary approach in a well supported referral centre is ideal. Although we can afford to be guardedly optimistic in prognosis, even in 1997 some families will opt to withdraw treatment, and this wish should be respected.

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