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An Epidemiological Analysis of CHARGE Syndrome: Preliminary Results From a Canadian Study

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CHARGE syndrome is a well-characterized clinical diagnosis with recent data supporting a genetic etiology. A 3-year national surveillance coordinated by the Canadian Pediatric Surveillance Program (CPSP) was started in September 2001. Physicians notified the CPSP if they had cared for individuals with CHARGE syndrome within their practice, and then completed a detailed reporting form. To date, there are 77 confirmed cases of CHARGE syndrome. The highest provincial prevalence of CHARGE syndrome in Canada was estimated at 1 in 8,500 live births. Subgroups of cases with particular clusters of anomalies were identified. In older individuals, bilateral posterior choanal atresia (BPCA) was predictive of the presence of the three other major criteria and of aortic arch anomalies. Individuals with CHARGE syndrome who demonstrated a less extensive phenotype ($\leq$3 major criteria) were more likely to present with minor cardiovascular malformations, including small atrial or ventricular septal defects (VSD) or patent ductus arteriosus (PDA). A significant cause of morbidity was severe feeding difficulty, including problems with chewing, swallowing, and gastroesophageal reflux, which were prevalent throughout childhood. Infant mortality is high in individuals with CHARGE syndrome. However, life expectancy has improved for those surviving their first year. Increased mortality was associated with distinct cardiovascular malformations or ventriculomegaly combined with brainstem or cerebellar anomalies. From this study, revised diagnostic criteria are proposed for infants, children, and adolescents to help identify a group of individuals who represent CHARGE syndrome with more of the classical features as apposed to the boarder association.

KEY WORDS: CHARGE syndrome; CHARGE association; CHARGE; bilateral posterior choanal atresia (BPCA); population-based study; epidemiological; incidence; diagnostic criteria; prevalence

INTRODUCTION

CHARGE syndrome is a rare disorder characterized by a combination of multiple congenital anomalies that occur together more frequently than would be expected on the basis of chance. Hall [1979] first described the association of choanal atresia and coloboma with other congenital anomalies in 17 children, suggesting that it might represent a multiple malformation syndrome. That same year Hittner described ten children with coloboma, congenital heart disease, and hearing loss. In 1981, the acronym CHARGE (*C*oloboma, *H*eart defects, *A*tresia choanae, *R*etarded growth and development, *G*enital hypoplasia, and *E*ar abnormalities) was coined by Pagon et al. [1981] The mnemonic was intended to capture the more common features of the association, and with time additional characteristic features have been added. In the last decade specific clinical criteria [Blake et al., 1998], and radiological features [Lemmerling et al., 1998] support the view of CHARGE as a syndrome rather than an association [Lubinsky, 1994]. Graham [2001] in his editorial explains the virtue of retaining both syndrome and association. In this epidemiological paper, we will use the acronym CHARGE to cover this specific syndrome of associated anomalies.

CHARGE is now recognized as one of the more common causes of dual sensory impairment leading to deafness with blindness [Strömland et al., 2003]. Other frequent neurological findings in such children are delayed motor development [Blake and Brown, 1993] and problems with balance [Lemmerling et al., 1998; Wiener-Vacher et al., 1999; Abadie et al., 2000]. Cranial nerve dysfunction resulting in difficulty with swallowing, chewing, and facial movement is also common in CHARGE [Lawand et al., 2003]. Autistic spectrum disorder was recently documented in 10/28 patients with CHARGE association followed in a prospective multidisciplinary study [Strömland et al., 2003], and the association between autistic spectrum disorder and CHARGE has recently been confirmed in other studies [Graham et al., 2004; Hartshorne et al., 2004; Smith et al., 2004].

The prevalence at birth of CHARGE has previously been estimated to range from 1 per 10,000 to 1 per 15,000 live births [Blake et al., 1998]. However, the actual incidence or

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prevalence of CHARGE in a population has never been determined. One epidemiological study identified 444 cases of choanal atresia among 5.43 million births ascertained through congenital malformation registries, for a birth prevalence of 0.82 cases of choanal atresia per 10,000 live births [Harris et al., 1997]. There were associated malformations in 44% of these cases of choanal atresia, of which 17% had three or more CHARGE malformations, and 51% had two or more CHARGE malformations. Clusters of anomalies associated with choanal atresia and coloboma were further explored in infants with multiple malformations tracked in registries in five countries [Källén et al., 1999]. Registries that only record those anomalies that can be detected shortly after birth may miss some of the most characteristic anomalies of CHARGE (distinctive middle and inner ears, retinal colobomata, cranial nerve defects, and temporal bone anomalies) limiting ascertainment.

Developing criteria for the diagnosis of CHARGE is difficult because there is wide variability in the clinical expression. Blake et al. [1998] suggested diagnostic criteria for CHARGE syndrome based on the frequency and specificity of a distinct set of anomalies (Table I). To qualify for the diagnosis of CHARGE, patients must exhibit all four major criteria, or three major and three minor criteria, or have a previous diagnosis of CHARGE and exhibit some of the major, minor, and occasional characteristics. Three distinct groups of CHARGE patients were ascertained: those with four major criteria, those with three major and three or more minor criteria, and those with fewer than three major criteria with substantial supporting evidence for a diagnosis of CHARGE. Compared to the classic characteristics captured in the "CHARGE" acronym, orofacial clefts were more important and congenital heart defects less salient as diagnostic criteria, a finding subsequently supported by epidemiological evidence [Källén et al., 1999].

Although most cases are sporadic, evidence to support a genetic basis includes: a 1%–2% recurrence rate among siblings born to parents not exhibiting features of CHARGE syndrome, suggesting possible germ cell line mosaicism, concordance in monozygotic twins and discordance in dizygotic twins, and advanced paternal age at conception among sporadic cases, suggesting possible fresh dominant mutations [Blake et al., 1993; Tellier et al., 1998]. There have been a variety of different chromosomal abnormalities identified in children with CHARGE syndrome, but there is no consistent pattern in the types of chromosomal anomalies. Recent studies using comparative genomic hybridization or microsatellite markers have failed to detect any chromosomal microdeletion [Sanlaville et al., 2002; Lalani et al., 2003]. Recently mutations in a new member of the chromodomain gene family (CHD7) have been identified in CHARGE individuals [Vissers et al., 2004].

TABLE I. The Diagnostic Criteria for CHARGE*

Major criteria
Coloboma—iris, retina, choroid, optic disc, or microphthalmia
Choanal atresia or stenosis—bilateral or unilateral
Ear anomalies—external, middle, or inner ear
Cranial nerve anomalies—facial palsy, dysphagia, sensorineural deafness
Minor criteria
Genital hypoplasia—micropenis and/or cryptochordism or hypoplastic labia
Congenital cardiovascular malformations of all types
Cleft lip
Tracheoesophageal fistula
Characteristic facial features—broad, sloping forehead, laterally protruding ears, small mouth, and high nasal bridge
Delayed motor, language, or global development
Occastional findings
Renal anomalies
Hand anomalies
Spine anomalies
Abdominal anomalies
Neck anomalies
Teeth anomalies
Immune anomalies

*Blake et al. [1998].

To date, most of the research concerning CHARGE syndrome has been based on case reports and single center studies. There are no published studies examining a national cohort of CHARGE individuals [but see Strömland et al., 2003]. In September 2001, we began a 3-year population-based study of all individuals with CHARGE syndrome in Canada. The objectives of this study were to determine the incidence and prevalence of CHARGE syndrome in Canada, to characterize subgroups of patients, and to identify factors that influence morbidity or mortality. Data were collected on paternal age as there have been reports of increased paternal age in CHARGE syndrome [Blake et al., 1993; Tellier et al., 1998]. Finally, a database of individuals born in Canada with CHARGE syndrome was compiled for future studies concerning developmental and behavioral aspects of this condition.

MATERIALS AND METHODS

Study Design

This was a population-based study conducted through a national surveillance coordinated by the Canadian Pediatric Surveillance Program (CPSP). The CPSP is an active real-time epidemiological surveillance tool for collecting pan-Canadian research data on low frequency high impact diseases and conditions. It utilizes a two-tiered active reporting process. Each month, the program sends a reporting form listing conditions under surveillance to nearly 2,350 pediatricians and pediatric subspecialists. Respondents indicate either new cases or "nil" reports. For each case report, the CPSP sends a follow-up detailed questionnaire. For 2003, the CPSP initial monthly response rate was 83%, while the detailed questionnaire completion rate was 96%. Results from the CPSP 2003 program evaluation confirmed that external validation was 89% for the congenital rubella syndrome study and 100% for cerebral edema in diabetic ketoacidosis and Creutzfeldt–Jakob disease. The positive predictive value was above 70% for all but two of the 17 studies. The CPSP undertakes surveillance of rare conditions whose reporting nationally would lead to improvements in their diagnosis, treatment, and prevention. Through these surveillances, the CPSP also aims to increase awareness of these uncommon disorders. The CPSP initiated a national survey of CHARGE syndrome patients in September 2001. Physicians notified the CPSP if they had cared for a CHARGE patient in their practice and completed a detailed reporting form (available on request from the authors), the information from which was compiled in a database. The reporting forms asked physicians to identify specific anomalies from a checklist for each patient, including the extent of visual and hearing impairment. There were also questions concerning behavioral problems, growth retardation, hormonal problems, delayed puberty, and feeding difficulties. Parental ages at the time of birth were requested. Ethical approval was obtained from the Research Ethics Board at the IWK Health Centre (Halifax, NS, Canada).

Case Definition

For each reported case, the diagnosis of CHARGE was confirmed by the principal investigator (KDB) using the diagnostic criteria of Blake et al. [1998]. Co-investigators (CP, JMG) were consulted if the diagnosis was uncertain. The

diagnostic criteria consisted of either four major or three major and three minor criteria (Table I). Children and adults with a previous diagnosis of CHARGE who exhibited some of the major, minor and occasional characteristics were also included in the study if the investigators agreed. Facial and ear photographs were requested for the children who were suspected of having CHARGE but there was insufficient information, i.e., as in a neonate or adult or there were less than three major criteria being met. This helped to determine if they had the characteristic facial features. Cases with a 22q11 deletion by fluorescence in situ hybridization (FISH) were excluded because a diagnosis of velocardiofacial syndrome was considered more likely [Scrambler et al., 1992].

Incidence Calculation

The birth prevalence of CHARGE Lubin calculated using the number of reported cases in which the birth date fell between January 1, 1999 and December 31, 2002. These years were used because it was believed that the number of reported cases would more closely resemble the actual number of CHARGE individuals born. The national and provincial birth rates most recent census figures were obtained from statistics Canada.

Subgroups Within the CHARGE Cohort

Individuals with CHARGE who exhibited all four major criteria were compared to individuals with three or fewer major criteria. The subgroups were also analyzed using the cardinal features of CHARGE: bilateral posterior choanal atresia (BPCA) and coloboma, and the frequencies of other associated features were examined.

Statistical Analysis

The data from all confirmed CHARGE cases were compiled in a database and analyzed using Fisher exact one-tailed *P* values, using the Epi Info 2001 epidemiological analysis package [Centers for Disease Control, Atlanta, GA].

RESULTS

Our study population of 77 was first compared to published cohorts of CHARGE patients (Table II). The frequencies of the major and minor features of CHARGE in this study resembled those in the published literature, with two differences: the characteristic facial appearance and the growth deficiency were less prevalent in our present study population. Moreover, anomalies that were previously considered to be only occasionally or rarely associated with CHARGE appeared to be relatively common in this study. For example, neck and shoulder anomalies, including a short or webbed neck or sloping shoulders, were noted in 35% of cases, while hand and spine anomalies were present in 14% and 9% of cases, respectively. These occasional anomalies were previously considered infrequent findings among CHARGE patients, possibly because their presence was not specifically ascertained as a feature of CHARGE in the earlier studies looking at younger patients.

Birth Prevalence

One major objective of this study was to estimate the prevalence of CHARGE syndrome. The average national birth prevalence of CHARGE syndrome was 3.5 per 100,000 live births. In Newfoundland and Labrador, and the Maritime Provinces (Nova Scotia, New Brunswick and Prince Edward Island), the incidences were 10.66 and 12.84, respectively per 100,000, this translates to a CHARGE occurrence of 1:8,500 live births in the Atlantic Provinces. However, in Alberta, one of the most populous provinces in Canada, no cases were reported of a child born with CHARGE during this time. (Table III)

Subgroups

CHARGE cases that exhibited all four major criteria (subgroup A) comprised 34% (26/77). Cases who exhibited three or fewer of the major criteria (subgroup B) were larger 66% (51/77) (Fig. 1). While cardiovascular malformations were very common in both groups, 57% of patients in subgroup A had a major cardiovascular malformation requiring surgery, compared to only 38% of those in subgroup B. Patients in subgroup A were more likely than those in subgroup B to exhibit the characteristic facial features of CHARGE (73 vs. 45%). There was also a trend toward an increased prevalence of facial palsy among those in subgroup A.

Bilateral posterior choanal atresia (BPCA) was reported in 28 of 77 individuals (36%) with choanal atresia. Fifteen of

TABLE II. The Frequencies of the Major and Minor Features of CHARGE in This Study Population and in the Literature

	N/total	Frequency (%)	Blake et al. [1998] (%)	Tellier et al. [1998] (%)
Major criteria				
Coloboma	59/77	77	80–90	79
Choanal atresia	49/77	64	50–60	57
Ear anomalies	74/77	96	90	100
Cranial nerves	70/77	91	70–90	N/A
Minor criteria				
Genital hypoplasia	29/77	38	N/A	34
Males	26/40	65	70–80	53
Female	3/37	8	N/A	16
Cardiac malformations	65/77	84	75–85	85
Cleft lip/palate	14/77	18	15–20	N/A
TE fistula	15/77	19	15–20	N/A
Characteristic face	42/77	55	70–80	N/A
Growth deficiency	45/77	58	70	75
Occasional findings				
Renal	28/77	36	15–25	N/A
Hand	12/77	16	Rare	N/A
Neck/shoulder	27/77	35	Rare	N/A
Abdominal	11/77	14	15%	N/A
Spine	7/77	9	Rare	N/A

TABLE III. Estimated Prevalence of CHARGE A/S in Canada

	Cases (no.)	Cases/year	Birth rate[a]	Prevalence/100,000 2001	Prevalence/100,000 2002
British Columbia	6	1.50	39,987	3.11	3.75
Alberta	0	0.00	37,517	0	0
Saskatchewan	3	0.75	11,896	1.99	6.30
Manitoba	4	1.00	13,940	7.06	7.17
Ontario	13	3.25	127,479	2.49	2.55
Quebec	8	2.00	72,397	1.75	2.76
Maritimes[b]	9	2.25	17,525	8.15	12.84[c]
Newfoundland	2	0.50	4,689	0	10.66[c]
Canada	45	11.25	327,187	2.73	3.44

Based on the number of CHARGE individuals born between 12/31/1998–12/31/2002.
Atlantic Provinces (New Brunswick, Prince Edward Island, Nova Scotia, and Newfoundland).
[a]Based on statistics Canada rates for 2001–2002.
[b]Maritimes = Nova Scotia, New Brunswick, and Prince Edward Island.
[c]This translates to 1:8,500 live births, in the Atlantic provinces, the highest reported incidence in the literature.

28 individuals (54%) with BPCA also had coloboma, and ear (external, middle, or sensorineural) and cranial nerve anomalies.

When individuals with BPCA were compared to those without BPCA, some differences were noted (Fig. 2). For individuals in subgroup B (three or fewer major criteria), the frequency of coloboma was lower for those with BPCA than among those not exhibiting BPCA [23% (3/13) vs. 79% (30/38)]. Anomalies of cranial nerves VII, IX, X, including difficulties with chewing and swallowing, were less common among those with BPCA. In subgroup A, the presence of BPCA was associated with a significantly lower frequency of chewing difficulties and swallowing problems ($P = 0.03$).

In our population, coloboma of the retina or choroid disk was by far the most common of the classical eye anomalies in CHARGE. These defects were present in 49 of 59 cases of coloboma (83%) and were bilateral in 41 of these cases (84%). Microphthalmia was also a frequent finding with 29% (17/59) reporting either bilateral or unilateral microphthalmia, this being associated with a coloboma of the retina or choroid disk in 10 of 17 cases (59%).

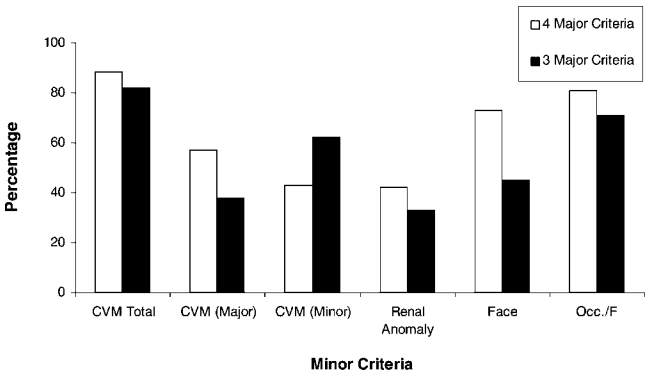

Fig. 1. The minor criteria in CHARGE individuals for study group (N = 77)—comparing subgroup A (four major criteria) versus subgroup B (three major criteria). Subgroup A, **light bars**; subgroup B, **dark bars**. CVM total: cardiovascular malformation—all; CVM (major): cyanotic cardiac malformation, AVSD, coarctation aorta; TOF, double outlet ventricle; CVM (minor): PDA, VSD, ASD; face: distinctive CHARGE facial features; Occ./F: occasional findings; major criteria in brief: coloboma, choanal atresia/stenosis, ear anomalies, cranial nerve dysfunction (VII, VIII, IX, XI)—a more detailed description is available from the reporting form on-line.

Cardiovascular Malformations

Eighty-four percent of patients (65/77) in this study had one or more of a wide variety of cardiovascular malformations (Table IV). The most common cardiac malformations included patent ductus arteriosus (PDA), atrial septal defects (ASD), and ventricular septal defects (VSD). Combinations of these three defects were present in 30% (14/42) of patients. Unfortunately the data collection methodology did not allow us to distinguish between the different types of ASD's and VSD's. Conotruncal defects and aortic arch anomalies were less frequent in our group than previously reported [Lin et al., 1987; Wyse et al., 1993; Tellier et al., 1998]. However, these malformations were frequent in patients within subgroup A. The highest prevalence of aortic arch anomalies was among patients in subgroup A, who exhibited BPCA (5/12, 42%), whereas no aortic arch anomalies were reported among the 12 individuals in subgroup A who exhibited unilateral choanal atresia or stenosis ($P = 0.095$). Conversely, there was a significantly increased prevalence of PDA ($P = 0.02$) and a trend toward an increased prevalence of VSD ($P = 0.06$) among those in subgroup B, as compared to subgroup A.

Morbidity and Mortality

Ten of the 77 reported cases (13%—six females and four males) were deceased. The age at time of death ranged from 5 days to 9 years with a mean of 14 months and a median of 11 weeks. Four patients died in the neonatal period, and five died between 1 and 12 months. The characteristics of each

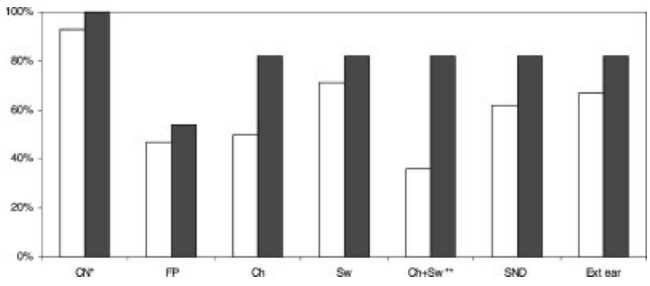

Fig. 2. Comparing the study population with all four major criteria based on the presence or absence of BPCA (bilateral posterior choanal atresia). **Light bars** represent cases with BPCA, **dark bars** represent cases not exhibiting BPCA. FP, facial palsy; Ch, chewing difficulties; Sw, swallowing difficulties; Ch + Sw, chewing and swallowing difficulties; SND, sensorineural deafness; Ext ear, external ear anomalies. *CN anomalies not including SND. **$P = 0.003$.

TABLE IV. Cardiovascular Malformations in CHARGE, Comparing Present Study With Past Studies

	Present study	Lin et al. [1987]	Wyse et al. [1993]	Tellier et al. [1998]
Number of patients	65	53	59	47
Conotruncal defects	11 (17%)	22 (42%)	17 (29%)	11 (27.5%)
Aortic arch anomalies	7 (11%)	9 (36%)	10 (17%)	2 (5%)
ASD	18 (28%)	2 (4%)	9 (15%)	3 (7.5%)
VSD	21 (32%)	2 (4%)	12 (20%)	5 (12.5%)
PDA	28 (43%)	12 (23%)	12 (20%)	8 (20%)
SVC anomalies	5 (8%)	0	0	0
AVSD	7 (11%)	3 (6%)	5 (8%)	N/A

ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; SVC, superior vena cava; AVSD, atrioventricular defect.

deceased patient are presented in Table V. None of these patients had all four major criteria. Four of ten patients had BPCA, of whom three died in the first week of life. In addition, eight of ten patients had major cardiovascular malformations. Conotruncal anomalies were more common in this group than in surviving CHARGE patients with congenital heart disease (33%, 3/9 vs. 12%, 7/56). Atrioventricular septal defects (AVSD) occurred in 44% (4/9) of deceased patients with cardiovascular malformations, as compared to 9% (5/55) among surviving individuals. When the frequency of AVSD among deceased individuals was compared to the frequency among surviving individuals, there was a statistically significant association between the presence of AVSD and mortality ($P = 0.02$).

Anomalies of the central nervous system, as diagnosed by computed tomography or magnetic resonance imaging, were documented in 7/10 (70%) cases (Table V). For the surviving population, brain imaging was completed in 57 individuals with 29 abnormal CTs or MRIs (29/57, 51%). For the deceased, ventriculomegaly and brainstem and/or cerebellar anomalies were most common. There were four cases of ventriculomegaly combined with cerebellar or brainstem anomalies among the deceased individuals, while only two cases were reported among the 57 surviving CHARGE patients. In comparing the frequency of this combination of anomalies in surviving versus deceased individuals, a significant association was found between the incidence of mortality and the occurrence of cerebellar and/or brainstem anomalies associated with ventriculomegaly ($P = 0.002$).

Feeding difficulties were a major cause of morbidity for individuals of all ages. Among deceased individuals, gastroesophageal reflux (GER) was present in 100% (6/6) of individuals older than 1 month at the time of death. In five of seven deceased individuals with GER (71%), the reflux was severe enough to require the placement of a gastrostomy tube.

Adolescents and Adults

Details of the 16 reported cases of adolescents and adults with CHARGE syndrome, details of which are presented in Table VI. Of these, 7/16 (44%) had BPCA; six of these seven cases (86%) also exhibited the other three major criteria. Only one individual with all four major criteria did not have BPCA. There was a significant correlation between the presence of BPCA and the occurrence of the three other major criteria ($P = 0.006$). Feeding problems were extremely common in this older CHARGE syndrome population among whom 88% (14/16) experienced various types of feeding difficulties at some point in their lives, with 62% (10/16) reporting GER. Placement of a gastrostomy tube was required in 50% (5/10) of these cases. Behavioral difficulties were reported in 75% (12/16) and pubertal delay in 67% (8/12) of those who had been assessed.

TABLE V. Deceased Patients With CHARGE

	Age at time of death	Sex	Choanal atresia	Cranial nerve dysfunction	Cardiovascular defects	Other anomalies	Feeding difficulties
1	<1 week	F	BPCA	Sw	TOF	H, A, N	GER, G-tube
2	7 weeks	M	—	—	PDA, ASD, TR	R, H, N	GER, G-tube
3	6.5 months	F	BPCA	Sw, SND	PDA, ASD	—	GER, G-tube
4	8 months	F	—	Ch, Sw, Rt FP, SND	TOF, AVSD	TEF, R	GER, vomiting
5	1 week	F	BPCA	—	PDA, abN TV and PV, RVH	F	—
6	4.5 months	F	CS	Ch, Sw	AVSD, absent PV	F	GER, aspiration, G-tube
7	2.5 months	M	CS	—	—	CP, F, H, N	GER, partial nasal obstruction
8	1 week	F	BPCA	SND	PS	TEF, R	TEF, G-tube
9	9 years	M	CA	Ch, Sw, Lt FP, SND	DORV, subaortic stenosis	CL, CP, F, R, N	GER, G-tube
10	2 weeks	M	—	—	DORV, AVSD, PS	F, N	—

BPCA, bilateral posterior choanal atresia; CS(A), choanal stenosis (atresia); TV(R), tricuspid valve (regurgitation); PV(S), pulmonary valve (stenosis); DORV, double outlet right ventricle; RVH, right ventricular hypertropy; CL/P, cleft lip/palate; F, characteristic facial features; R, renal anomalies; H, hand anomalies; A, abdominal defects; N, neck/shoulder anomalies; TEF, trachesophageal fistula, GER, gastroesophageal reflux.

TABLE VI. Adolescents and Young Adults With CHARGE

ID	Sex	Coloboma	Choanal atresia	Ear anomalies	Cranial nerve dysfunction[a]	Feeding difficulties	Behavior	Endocrine
A1	F	Rt Mo	BPCA	Ext, Bil SND	Ch, FP	GER	—	SS, DP
A2	F	Bil IC and RC	BPCA	Ext, Mid	Ch, Sw, V	dysph	OC	SS, DP
A3	F	Rt Mo	—	Mid, Bil SND	Ch, V	Due to CL/P	HA, OC	SS, DP
A4	M	Rt IC, Rt RC	—	—	Ch, Sw, Bil FP, V	GER	HA, Sl	—
A5	F	Bil RC	CA	Ext, Bil SND	Ch, Sw	GER, G-tube	—	—
A6	M	Bil RC	BPCA	Ext, Mid, Bil SND	—	—	—	SS, DP
A7	M	Bil RC	—	Mid	Sw	GER, G-tube	HA, OC	DP
A8	M	Bil RC	—	Ext, Mid, Bil SND	Ch, Sw, FP, V	GER, G-tube	Sl, OC	GHD, DP
A9	M	Lt IC, Bil Mo	—	Ext, Mid, Bil SND	Ch, Sw, V	Not specified	Sl, OC	SS, DP
A10	M	—	CA	Ext, Mid, Bil SND	Ch, Sw, V	GER, G-tube, PPD	—	SS, GHD, DP
A11	M	Bil RC	—	Ext, Mid, Bil SND	FP, Sw	Not specified	HA, Sl	SS, GHD, DP
A12	M	Rt IC, Bil RC, Rt Mo	—	Ext, Mid, Bil SND	Ch, Sw, FP	GER	HA	SS
A13	F	Bil RC, Rt Mo	BPCA	Ext, Mid, Bil SND	Ch, Sw, FP	GER	HA, OC	DP
A14	M	—	BPCA	Ext, Mid	FP, V	GER	HA, Sl, OC	—
A15	F	Bil RC	BPCA	Ext, Mid, Bil SND	Sw	—	—	SS, GHD, DP
A16	F	—	BPCA	Mid	—	GER, G-tube	—	SS

Mo, microphthalmia; Bil, bilateral; IC, coloboma of the iris; RC, coloboma of the retina or choroids; CA, choanal atresia; Ext, external ear anomalies; Mid, middle ear anomalies; V, vestibular problems; Sw, swallowing problems and dysphagia; CL/P, cleft lip/palate; PPD, palatopharyngeal dyskinesia; OC, obsessive and/or compulsive behavior; HA, hyperactivity; Sl, sleep problems; SS, short stature (below the 5th centile); DP, delayed puberty; GHD, growth hormone deficiency.
[a]Excluding SND (sensory neural deafness).

Parental Age

The mean maternal age at the time of birth of individuals with CHARGE syndrome was 29.1 ± 5.9 (SD) years ($N = 62$), and the mean paternal age was 32.4 ± 4.2 years ($N = 43$). Among those in subgroup A, the mean paternal age was 33.6 ± 4.9 years ($N = 16$), while the mean paternal age among those in subgroup B was 31.7 ± 4.4 years ($N = 26$). The median paternal age also differed between the two subgroups (32.5 years for subgroup A and 30.8 for subgroup B); however, in both subgroups, only slightly more than 30% of fathers were 34 years of age or older (33% vs. 31%).

DISCUSSION

To date the surveillance indicates that 77 individuals with confirmed CHARGE have been reported in Canada. This represents one of the largest CHARGE cohorts in the literature. There are several distinct differences between the data from the present population-based study and other data in the literature. One important difference is the lower frequency of major cardiovascular malformations, including conotruncal and aortic arch defects, in the present study [Lin et al., 1987; Wyse et al., 1993; Tellier et al., 1998]. Furthermore, many features that were not previously associated with CHARGE, such as renal and neck anomalies appear to be much more common than previously reported [Blake et al., 1998]. This study has attempted to describe in detail the range of presentation of CHARGE, from mild to severe.

Birth Prevalence

There is distinct provincial and regional variation in the reported birth prevalence of CHARGE in Canada. It is unlikely that this is due to an environmental factor. Rather, the variation is likely due to increased interest and experience regarding CHARGE syndrome in the Atlantic Provinces (Maritimes and Newfoundland) and Manitoba, resulting in increased awareness and higher reporting rates. The true incidence of CHARGE syndrome may therefore approach the Atlantic Provinces' figure of 1 per 8,500 live births, a higher occurrence than previously estimated [Blake et al., 1998]. Efforts are underway to contact geneticists and specialists in areas with low reporting rates in order to increase the ascertainment of individuals with CHARGE.

Subgroups

Identifying a syndrome within the CHARGE population in this study has proved difficult. While the presence of all four major criteria was thought to identify those with a more severe phenotype of CHARGE, this does not seem to be the case. There were only a few differences in the other associated anomalies between those with all four (subgroup A) and those with fewer than four (subgroup B) major criteria. Although it is considered a classical feature of CHARGE, BPCA is not necessarily associated with either the presence of the four major criteria or the presence of more of the minor and occasional criteria. BPCA is considered highly suggestive of CHARGE. Thus, it is possible that some patients with BPCA may have been diagnosed with CHARGE even though they have fewer associated anomalies. Among adolescents and young adults (ages 12–25), BPCA was significantly associated with the presence of the other three major criteria. Thus, the presence of BPCA may suggest the co-existence of other major anomalies, some of which may be diagnosed only later in childhood. These findings could also be attributed to the fact that in older CHARGE syndrome individuals, the original diagnosis was based on earlier diagnostic criteria, and use of the CHARGE acronym for diagnosis might have selected for those with a more severe phenotype.

In our population, minor heart defects such as PDA, VSD, and ASD were much more common than in the literature, while the conotruncal and aortic arch anomalies were less common. Some previous studies of cardiovascular malformations in CHARGE syndrome used the tertiary cardiology centers for identifying patient populations. These studies may not have ascertained a

sub-population with minor or no heart defect, if the patients had not been followed at a tertiary cardiology center.

Conotruncal and aortic arch defects and AVSDs, however, were more common among those individuals with a severe presentation of CHARGE (subgroup A). The presence of BPCA, in addition to coloboma, ear, and cranial nerve anomalies, was significantly associated with an increased incidence of aortic arch anomalies. Conversely, a less severe presentation of CHARGE (subgroup B) was correlated with a higher frequency of minor cardiovascular malformations, particularly PDA and VSD.

Morbidity and Mortality

This study confirmed previous findings [Blake et al., 1990; Tellier et al., 1998] that patients who survive infancy will tend to survive through childhood. The deceased patient population did not appear more likely to exhibit the more severe phenotype of CHARGE (subgroup A). However, one explanation for this could be that some patients had additional anomalies that had not been diagnosed due to their young age.

Two studies have reported factors that increase mortality among individuals with CHARGE [Blake et al., 1990; Tellier et al., 1998]. Males have previously been reported to have an increased mortality over females [Blake et al., 1990; Tellier et al., 1998], but our results do not support this conclusion, as 40% of deceased patients were male. Other factors that have been associated with increased mortality are midline central nervous system malformations [Tellier et al., 1998], cyanotic cardiovascular malformations [Blake et al., 1990], tracheoesophageal-fistula (TEF), and BPCA [Blake et al., 1990; Tellier et al., 1998]. In one study, 85% (11/13) of patients who were deceased had two or more of the following anomalies: BPCA, TEF, and cyanotic cardiovascular malformations [Blake et al., 1990]. In the present study, only two of ten deceased patients (20%) had 2 of the above anomalies, while six patients had one anomaly and two patients had none. We conclude that during the last decade, individuals with CHARGE syndrome have benefited from improvements in diagnosis and treatment of certain anomalies, in particular, major cardiovascular malformations.

The factors associated with increased mortality in the present study were the presence of AVSD and cerebellar and/or brainstem anomalies associated with ventriculomegaly. It is unclear why AVSD was significantly associated with an increase in mortality while other major cardiovascular malformations were not. Conotruncal defects, specifically double-outlet right ventricle and tetralogy of Fallot, occurred somewhat more among those patients who were deceased, although this difference was not statistically significant. The combination of cerebellar or brainstem anomalies with ventriculomegaly has not been previously reported as a factor for mortality in CHARGE syndrome. Previous studies have found forebrain and midline defects to be more common than hindbrain anomalies or hydrocephalus [Lin et al., 1990; Tellier et al., 1998]. Further study of a larger cohort of deceased individuals is needed to determine the significance of these mortality factors.

This study identifies the high prevalence of feeding difficulties among individuals with CHARGE of all ages. We suggest that feeding issues are a significant morbidity issue for CHARGE individuals. These problems present challenges for the management of these patients, and may contribute to mortality. A total of 90% (9/10) of deceased patients were at risk for aspiration or pharyngeal incoordination due to GER, TEF, or swallowing and chewing difficulties, which was previously reported as a common cause of death [Blake et al., 1990]. A significant limitation of this study is that detailed reports of the cause of death were not available to us.

Adolescents and Adults

Issues for older individuals with CHARGE include behavioral problems and endocrine deficiencies, particularly hypogonadism. We recommend that an endocrinologist follow these patients from early childhood, through puberty and into adult life to address issues related to persistent hypogonadism, such as osteoporosis and obesity [Abi Daoud et al., 2002; Blake et al., 2004; Searle et al., 2004].

Paternal Age

Our paternal data is only 55% complete and therefore the trend in higher paternal age for individuals expressing all four major criteria needs to be interpreted with some caution.

The overall mean paternal age in this study is lower than that previously reported [Blake and Brown, 1993; Tellier et al., 1996], paternal age varied among subpopulations. The mean and median paternal ages were slightly higher among CHARGE individuals with all four major criteria as compared to those with three or fewer major criteria. This suggests that advanced paternal age may be associated with a more severe presentation of CHARGE.

Refining the Diagnostic Criteria

There may be a characteristic CHARGE clinical presentation that becomes more evident as individuals mature.

We propose a refinement of the previous diagnostic criteria [Blake et al., 1998] to capture the continuum of the CHARGE syndrome presentation, (similar to the Prader–Willi classification [Gunay-Aygun et al., 2001]) to address the implications for diagnostic practice. The proposed major criteria for newborns and infants are similar to the 1998 criteria, but have been refined to include: Coloboma of the retina or choroid, choanal atresia (BPCA), cranial nerve dysfunction leading to asymmetric facial palsy and/or swallowing/feeding difficulties, and characteristic external ears (absent or hypoplastic lobes, asymmetry, decreased cartilaginous folds, and triangular concha) and inner ear anomalies (temporal bone findings with cochlear hypoplasia and or absent/hypoplastic semicircular canals). Minor criteria include coloboma of the iris, unilateral choanal atresia and/or stenosis, genital hypoplasia, and cardiovascular malformations.

We recommend consistent use of CT or MRI scans of the head with associated temporal bone imaging to detect choanal atresia or stenosis, temporal bone anomalies, and ventriculomegaly to facilitate making the CHARGE diagnosis.

In children aged 1–11 years, the proposed major criteria for infants (as above) would apply with the addition of sensorineural hearing loss, the assessment of which is often inconclusive before 1 year, vestibular and balance problems (may result in delayed walking), feeding difficulties requiring medical and surgical intervention [Blake and Brown, 1993], growth deficiency [Blake et al., 1993].

In adolescents and adults, pubertal delay due to hypogonadotropic hypogonadism, and osteoporosis [Abi Daoud et al., 2002] would be added to the criteria. Although at present, most individuals with CHARGE syndrome are diagnosed within the first weeks of life, these criteria will help to identify the older CHARGE syndrome population and allow physicians caring for these individuals to anticipate issues that may arise as the child matures.

LIMITATIONS

We assume that there was significant underreporting of CHARGE syndrome in certain regions of Canada. Thus our initial findings may not represent a complete picture of the CHARGE syndrome population in Canada. Moreover, there

are only 13 reported cases of adolescents, and three reports of young adults, so it is quite possible that many adults and adolescents with CHARGE syndrome have never been diagnosed or that they cannot be located through pediatricians. The age range of individuals at the time of diagnosis was several years for those born prior to 1990, but this has dropped to the first weeks of life for those born between 1997 and 2001. A second consideration is that more patients are surviving through infancy and childhood now than in the past, and both factors may contribute to this finding.

Another limitation is that details of the specific anomalies exhibited by each patient were obtained from checklist forms completed by the reporting physician. In many cases, the forms were partially incomplete because physicians did not have all the details of their patient complex medical histories. Multiple reports by different subspecialists concerning the same patient, as well as information provided by the families of individuals with CHARGE syndrome (with consent), helped to complete the records. Nonetheless, information was still lacking in some areas, particularly regarding paternal age. Furthermore, some clinical findings are subjective and despite our best efforts, the reporting of such findings was not standardized, but dependent instead on the clinical judgment of individual physicians. Therefore, there may have been some inconsistency in the reporting of such findings.

CONCLUSIONS

The present study provides a picture of the range of CHARGE within a population. This study population, larger than any in the literature, helps to further characterize CHARGE by identifying factors that influence mortality, as well as describing co-occurrence of anomalies. Refining the diagnostic criteria is an important step in the characterization of a distinct syndrome within the CHARGE association, which one of us has termed the Hall–Hittner Syndrome [Graham, 2001]. The Canadian Pediatric Surveillance Program (CPSP) will continue to survey for individuals with CHARGE until September 2004. We will apply the proposed revised diagnostic criteria, as well as the existing criteria, to the total study population. This will allow the continued investigation of etiological factors and identification of a cohort suitable for a longitudinal evaluation of factors influencing morbidity and developmental outcome.

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