

## Original Article

# Death in CHARGE syndrome after the neonatal period

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CHARGE syndrome is a multiple congenital anomaly syndrome that can be life-threatening in the neonatal period. Complex heart defects, bilateral choanal atresia, esophageal atresia, severe T-cell deficiency, and brain anomalies can cause neonatal death. As little is known about the causes of death in childhood and adolescence, we studied post-neonatal death in patients with CHARGE syndrome. We collected medical data on three deceased children from a follow-up cohort of 48 CHARGE patients and retrospectively on an additional four deceased patients (age at death 11 months to 22 years). We analyzed the factors that had contributed to their death. In five patients respiratory aspiration had most likely contributed to premature death, one died of post-operative complications, and another choked during eating. From our findings and a literature review, we suggest that swallowing problems, gastro-esophageal reflux disease, respiratory aspiration and post-operative airway events are important contributors to post-neonatal death in CHARGE syndrome. Cranial nerve dysfunction is proposed as the underlying pathogenic mechanism. We recommend every CHARGE patient with feeding difficulties to be assessed by a multidisciplinary team to evaluate cranial nerve function and swallowing. Timely treatment of swallowing problems and gastro-esophageal reflux disease is important. Surgical procedures on these patients should be combined whenever possible because of their increased risk of post-operative complications and intubation problems. Finally, we recommend performing autopsy in deceased CHARGE patients in order to gain more insight into causes of death.

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CHARGE syndrome is a congenital malformation syndrome that occurs in approximately 1/10,000 live births (1, 2). CHARGE (OMIM 214800) is an acronym for coloboma, heart defects, atresia of choanae, retardation of growth and development, genital abnormalities, and ear anomalies (including deafness) (3). Arhinencephaly, hypoplasia of semicircular canals, and cranial nerve (CN) palsies are also present in the majority of patients (2, 4–6). Occasional features include esophageal atresia, cleft lip/palate, renal abnormalities, and

hypogonadotropic hypogonadism (2). The genetic etiology of CHARGE syndrome was clarified in 2004, when mutations in the chromodomain helix case DNA binding protein 7 (*CHD7*) gene were described (7).

Some of the congenital abnormalities present in CHARGE syndrome can lead to premature death. Abnormalities that can be life-threatening in the neonatal period are complex heart defects, bilateral choanal atresia, esophageal atresia, severe T-cell deficiency, and brain anomalies (1, 8–11).

However, from clinical practice, we know that a significant percentage of children with CHARGE syndrome die after the neonatal period (with post-neonatal period defined as 28 days or older). Death is sometimes related to surgical procedures or major congenital abnormalities, but occasionally it occurs suddenly and unexpectedly. Previous studies have described the clinical features in large series of patients with CHARGE syndrome, but did not give details on causes of death (1, 8, 9, 12, 13). We have, therefore, focused on causes of death in patients with CHARGE syndrome that died after the neonatal period. We collected medical data on three deceased children from a follow-up cohort of 48 CHARGE patients and retrospectively on additional four deceased patients. Based on our findings we propose recommendations to prevent premature death in patients with CHARGE syndrome.

### Patients and methods

We studied a cohort of 48 patients with CHARGE syndrome who were seen at the multidisciplinary CHARGE outpatient clinic in the Netherlands between 2005 and 2009. The mean age at first admission to the CHARGE outpatient clinic was 11 years 8 months (range 4 months–49 years). All 48 patients (21 females, 27 males) had definite CHARGE syndrome, 46 had a *CHD7* mutation [*CHD7* analysis as described in Ref 12] and the other two patients fulfilled the clinical criteria described by Blake or Verloes (14, 15). Three of the patients in this cohort died at age 11.5 months, 8 years, and 22 years. These data were used to produce a Kaplan–Meier actuarial survival curve.

In addition, we collected the medical data of a further four patients with CHARGE syndrome that had died after 11 months of age. These patients were identified through the Dutch patient organization ( $n = 1$ ), through the database of the Department of Genetics, University Medical Center Groningen ( $n = 1$ ), and through the Canadian database of CHARGE patients (Prof. K. Blake,  $n = 2$ ). All patients either fulfilled the clinical criteria for CHARGE syndrome postulated by Blake or Verloes (14, 15) and/or had a pathogenic *CHD7* mutation. The 22q11 deletions were excluded in all patients by fluorescent *in situ* hybridization (FISH) analysis and all karyotypes were normal. The parents of the Dutch patients gave informed consent to release the medical records and for publishing photographs. Ethical consent was granted by the IWK Health Centre for chart review of the Canadian patients.

In the surviving patients of 10 years and older from the CHARGE outpatient clinic ( $n = 25$ ), we scored the clinical features that were present in their first 10 years of life. We compared these features with the features of the six patients that died before 10 years of age (two patients from the CHARGE outpatient clinic and four patients from other centers). We tried to identify possible risk factors for premature death. One of the factors we scored was feeding difficulties, which we defined as feeding problems necessitating tube feeding (at present or in the past). Breathing difficulties were scored if patients had had a tracheotomy or needed extra oxygen. A  $\chi^2$ -test was performed to identify significant differences between the two groups (significance level 0.05).

### Results

The demographics, results of *CHD7* analysis, scores on Blake's and Verloes' criteria, and the clinical details of the seven deceased patients with CHARGE syndrome are summarized in Table 1. A Kaplan–Meier actuarial survival curve is presented in Fig. 1, showing the incidence of premature death among patients with CHARGE syndrome, who were seen in the multidisciplinary CHARGE outpatient clinic in the Netherlands. Three of these patients died at the ages of 11.5 months, 8 years, and 22 years, respectively, giving an actuarial post-neonatal survival of 98% at 1 year of age, 95% at 10 years of age, and 76% at 25 years of age. We would like to stress that this survival curve only applies to patients, who survived the neonatal period, as that is the population of the CHARGE outpatient clinic.

#### Patient A

Patient A (Fig. 2A) had esophageal atresia, ventricular and atrial septal defects, and brain anomalies (hypoplasia of cerebrum/cerebellum, small pons). He received tube feeding until he was two years old and underwent fundoplication for gastroesophageal reflux disease (GERD). He had recurrent aspiration pneumonias. He ingested solid food rapidly but experienced problems with swallowing liquids. His parents described him as a voracious eater. A barium swallow was advised, but before this could take place he died unexpectedly while eating when he was 8 years old. His mother heard labored breathing and saw he was choking. She was not able to free the airway; Heimlich maneuver and resuscitation were not successful. Intubation by the emergency team failed.

Table 1. Clinical features of seven deceased patients with CHARGE syndrome<sup>a</sup>

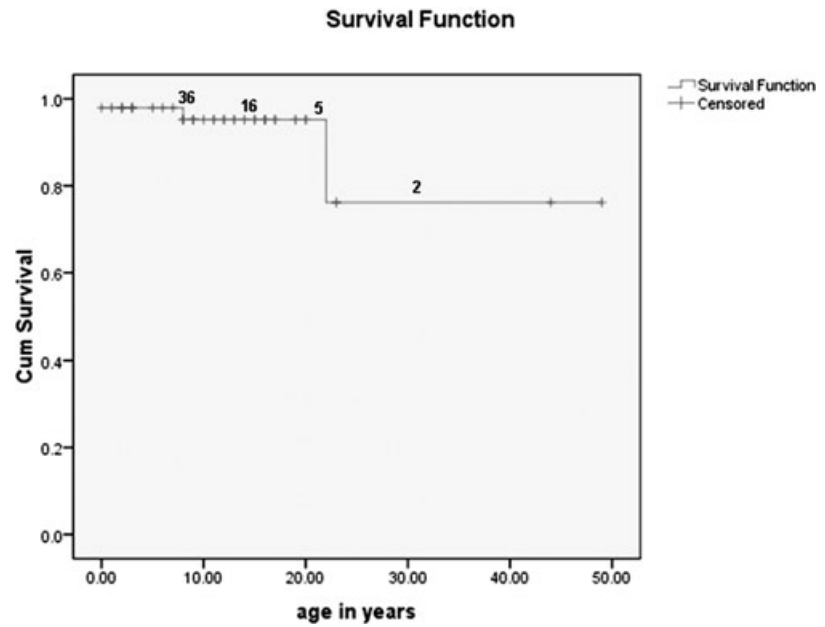
Child	Sex	Age at death	CHD7 mutation	Clinical criteria <sup>b</sup>		CHARGE features	Cranial nerve dysfunction	Features contributing to premature death	Cause of death
				Blake	Verloes				
A	M	8 y	+ (fs)	-	- <sup>c</sup>	H, G, E	III, VII, VIII, IX-X	FD, GERD, RA, SGS, TE	Fatal choking on food
B	M	22 y	+ (fs)	+	+	C, R, G, E	VII, VIII, IX-X	CP, FD, GERD, RA	Diagnosed with pneumonia: respiratory aspiration or circulatory arrest?
C	M	11.5 m	+ (fs)	+	+	C, A, G, E	VII, IX-X	FD, GERD, LM	Diagnosed with viral respiratory tract infection: respiratory aspiration or circulatory arrest?
D	M	14 m	U	+	a <sup>c</sup>	C, H, R, G, E	VIII, IX-X	FD, GERD, RA, TE	Respiratory aspiration or circulatory arrest?
E	F	27 m	U	+	+	C, H, A, R, E	IX-X	FD, GERD	Respiratory aspiration?
F	M	9 y	U	+	+	C, H, A, R, G, E	V, VII, VIII, IX-X	CLP, FD, GERD	Respiratory aspiration?
G	M	14 m	+ (non)	+	+	C, H, A, R, G, E	IX-X	CP, FD, GERD, RA, SGS	Post-operative complications

F, female; M, male; m, months; y, years; fs, frame shift mutation (c.1820\_1821insTTGT, p.Ala608fs; c.4779del, p.Gln1595fs; c.6835del, p.Ala2279fs); non, nonsense mutation (c.934C>T, p.Arg312X); U, unknown; a, atypical CHARGE patient; C, coloboma; H, heart defect; A, atresia or stenosis of choanae; R, retardation of growth and/or development; G, genital hypoplasia; E, ear anomalies or deafness; III, oculomotor nerve palsy; V, trigeminal nerve palsy; VII, facial nerve palsy; VIII, sensorineural hearing loss; IX-X, swallowing problems; CLP, cleft lip and palate; CP, cleft soft palate; FD, feeding difficulties; GERD, gastro-esophageal reflux disease; LM, laryngomalacia; RA, respiratory aspiration; SGS, subglottic stenosis; TE, tracheo-esophageal problems.

<sup>a</sup>Cases were identified through the CHARGE outpatient clinic (cases A-C), through the database of the Department of Genetics, University Medical Centre Groningen (case D), through the Canadian database (cases E and F) and through the Dutch patient organization (case G).

<sup>b</sup>Positive (+) or negative (-) for clinical criteria.

<sup>c</sup>Semicircular canal imaging not performed.



*Fig. 1.* Kaplan–Meier curve. Kaplan–Meier post-neonatal actuarial survival of 48 patients with CHARGE syndrome. Along the curve is the number of patients that were still being followed up at the Dutch CHARGE outpatient clinic.

In the hospital (90 min later), secondary respiratory aspiration was seen. Because of the deteriorated respiratory and neurological condition, resuscitation was stopped. The cause of death was fatal choking on food. No autopsy was performed.

#### Patient B

Patient B (Fig. 2B) had neonatal convulsions. He suffered from recurrent aspiration pneumonias and respiratory insufficiency, which necessitated a tracheotomy until he was 10 years old. He was fed by a G-tube and fundoplication was performed because of GERD. The day before his death, at age 22 years, he was diagnosed with pneumonia and given antibiotic treatment. The next evening, his condition seemed to have improved, but he died unexpectedly while lying on his bed. Although some vomit was found, his parents did not have the impression that he had aspirated. Autopsy was not performed and cause of death is unknown. He may have died of respiratory aspiration or cardiac arrest.

#### Patient C

Patient C (Fig. 2C) had neonatal convulsions and brain anomalies (enlarged ventricles, abnormal pons). For several days a Mayo tube was needed because of respiratory problems (unilateral choanal atresia and laryngomalacia). He was fed by a G-tube and had GERD. A barium swallow was performed a few days before his death, showing abnormal swallowing movements and nasal regurgitation. At age 11.5 months, a viral

upper respiratory tract infection was diagnosed and within 48 h he died unexpectedly during the night. When his parents found him, he had a pink color and was still warm; resuscitation was unsuccessful. No autopsy was performed and the cause of death is unknown. It was speculated that he died from respiratory aspiration or circulatory arrest (myocarditis or arrhythmia).

#### Patient D

Patient D (Fig. 2D) had esophageal atresia, a congenital heart defect (Fallot's tetralogy, aberrant course of subclavian artery, and aorta and a dysplastic pulmonary valve), and brain anomalies (polymicrogyria and abnormal cerebellum). In addition, on ECG examination supraventricular tachycardias were recorded. He suffered from recurrent aspiration pneumonias and received tube feeding. Fundoplication was performed for GERD. When he was 13 months old, surgical correction of the Fallot's tetralogy was performed. The surgery and the post-operative stay in the hospital were uneventful and after 4 weeks he was discharged in good condition. A few days later, his parents found him dead in his bed at night (age at death–14 months). No autopsy was performed and the cause of death is unknown. He may have had an arrhythmic event, but this remains speculative without monitoring. In general, supraventricular arrhythmias do not cause sudden death at this age. It is also possible he died from respiratory aspiration.



*Fig. 2.* Photographs of deceased patients with CHARGE syndrome. (A) Patient A at age 7 years 6 months, with strabismus, broad short neck and low set dysmorphic ears with triangular conchae and absent ear lobes. (B) Patient B at age 20 years 10 months, with strabismus, left facial palsy, deviated nose and bilateral cup ears. (C) Child C at 3 months of age, showing a square face with small chin and low set dysmorphic ears without lobes. (D) Child D at 1 month (left) and 6 months of age showing strabismus and dysmorphic ears. (G) Child G at 3 months of age, showing a square face with small chin and dysmorphic ears.

#### Patient E

Patient E had Fallot's tetralogy and bilateral choanal atresia. She had a G-tube for severe feeding problems and GERD. She died at age 27 months. The cause of death is unknown, but it was thought that severe GERD led to respiratory aspiration and therefore played a major role in her death. No autopsy was performed.

#### Patient F

Patient F had seizures and a complex heart defect (double outlet right ventricle, sub-aortic stenosis and ventricular septal defect). A G-tube was inserted at the age of 15 months because of feeding problems and withdrawn when he was 5 years old. The presence of GERD led to a fundoplication procedure. He suffered from recurrent bowel obstructions and sepsis, which was also the reason for his final admission to the

hospital. After recovery from the bowel sepsis, he died suddenly during hospitalization at age 9 years. No autopsy was performed; as the bowel sepsis was no longer a problem at the time of death, other issues such as respiratory aspiration, were cited as contributing to his death.

#### Patient G

Patient G (Fig. 2G) was born with bilateral choanal atresia, a complex heart defect (double outlet right ventricle, pulmonary valve stenosis and ventricular septal defect) and brain abnormalities (hypoplasia of the vermis, enlarged ventricles). Feeding difficulties and recurrent aspiration pneumonias required insertion of a G-tube. He underwent fundoplication surgery for GERD. At the age of 13 months, he had cardiovascular surgery complicated by post-operative respiratory problems, propofol intoxication, hypertriglyceridaemia,

Table 2. Comparison of features of surviving and deceased patients with CHARGE syndrome

Features	Surviving patients $\geq$ 10 years		Patients who died < 10 years		Comparison p-value <sup>e</sup>
	n = 25	%	n = 6	%	
Male gender	12/25	48.0	5/6	83.3	NS
Bilateral choanal atresia	5/25	20.0	1/6	16.7	NS
Congenital heart defect	7/25	28.0	5/6	83.3	0.022
TE anomaly	1/25	4.0	2/6	33.3	NS
Breathing difficulties <sup>a</sup>	8/24 <sup>c</sup>	33.3	4/6	66.7	NS
Brain malformation	13/17 <sup>d</sup>	76.5	4/4 <sup>d</sup>	100.0	NS
GERD	6/24	25.0	6/6	100.0	0.002
Feeding difficulties <sup>b</sup>	14/24	58.3	6/6	100.0	NS
Epilepsy	3/24	12.5	1/6	16.7	NS
Breathing + feeding difficulties + GERD	4/24	16.7	4/6	66.7	0.029
Breathing + feeding difficulties	7/24	29.2	4/6	66.7	NS

NS, not significant.

<sup>a</sup>Breathing difficulties: patient had needed oxygen or tracheotomy.

<sup>b</sup>Feeding difficulties: patient had required (short- or long-term) tube feeding.

<sup>c</sup>Information on this specific feature was unknown in one patient, who was therefore not included in the analysis.

<sup>d</sup>Brain scans were performed in only 17/25 surviving patients and in 4/6 deceased patients.

<sup>e</sup>p-value ( $\chi^2$ -test, univariate analysis).

liver and kidney function disturbances, sepsis, and hypotension. He developed a severe post-hypoxic encephalopathy with cerebral atrophy. Contact was no longer possible and from then on he received only palliative treatment. He died at age 14 months. No autopsy was performed.

We compared the features of the survivors aged 10 years and older ( $n = 25$ ) with the patients who died before they were 10 years old ( $n = 6$ ) (Table 2). The most striking difference was seen for GERD, which was present in all the deceased patients, but only in 25% of survivors before the age of 10 years ( $p = 0.002$ ,  $\chi^2$ -test, univariate analysis). The combination of breathing and feeding difficulties with GERD was also significantly more often present in the deceased patients ( $p = 0.029$ ). Apart from congenital heart defects ( $p = 0.022$ ), none of the other clinical features was significantly over-represented in the deceased patients.

### Discussion

Post-neonatal demise is an under-estimated complication in patients with CHARGE syndrome. In our prospective cohort of 48 patients with CHARGE syndrome, three patients died after 11 months of age, resulting in an actuarial post-neonatal survival of 95% and 76% at the ages of 10 and 25 years, respectively (Fig. 1). This percentage is in line with previous studies that reported mortality rates between 7.5% and 30% in CHARGE patients older than one year (8, 11, 16,

17). It must be noted that our prospective cohort (from the Dutch CHARGE outpatient clinic) is biased. Very severely or very mildly affected patients are often under-represented in this kind of multidisciplinary clinics and some very severe cases may have already died at a young age. Therefore, this survival curve only applies to patients who survived the neonatal period.

In this study, we describe seven cases of post-neonatal death. In most of these, death occurred suddenly and unexpectedly. In five patients the cause of death was likely attributable to respiratory aspiration and/or circulatory arrest. One patient choked during eating and another patient died after post-operative complications. Our observations are in line with a previous study that reported the causes of death in five patients with CHARGE syndrome older than one year to be circulatory arrest ( $n = 2$ ), respiratory aspiration ( $n = 2$ ) and post-operative complications ( $n = 1$ ) (17). Two other studies (8, 11) proposed respiratory aspiration as a major cause of mortality. Our study supports this theory, with respiratory aspiration likely contributing to early death in 5/7 patients (Table 1). However, due to the predominantly retrospective nature of our study and the lack of autopsy data, the cause of death remains speculative in five patients. It is possible that other causes may have contributed to death, like congenital heart defects (present in 3/5 patients), brain abnormalities (present in the two patients who had a cerebral magnetic resonance imaging (MRI) scan of these five patients), epilepsy (1/5), or esophageal atresia (1/5).

Unlike respiratory aspiration, choking has not been reported before as the cause of premature death in CHARGE syndrome. We presented the tragic history of patient A, who choked during eating when he was 8 years old. A major risk factor for choking is status post-repair of esophageal atresia, but subglottic stenosis, swallowing difficulties, and voracious eating behavior could also have contributed to his death (18–20).

Perioperative complications are another important cause of death in post-neonatal CHARGE syndrome patients. Post-operative mortality rates are higher in patients with CHARGE syndrome than in the general population. As patients with CHARGE syndrome generally have to undergo several surgical procedures, this risk should not be underestimated (8). Patients with airway malformations, severe feeding difficulties and GERD have a high risk of post-operative complications. Cardiovascular surgery in particular seems to pose the highest risk. Post-operative airway events occur after 35% of anesthetic procedures in CHARGE syndrome (21). It has been hypothesized that CN defects might underlie post-operative airway problems, as these nerves play an important role in the proper handling of oral secretions (which are increased after anesthesia) (21). Problems can also occur pre-operatively, as intubation problems are often seen in patients with CHARGE syndrome. This is mainly due to congenital airway malformations (choanal atresia, cleft lip/palate, micrognathia in combination with an anterior larynx, subglottic stenosis, and laryngeal clefts) (22, 23).

GERD, feeding/breathing difficulties and congenital heart defects were identified as risk factors for early death in our outpatient clinic population. On comparing the features of the surviving patients of 10 years and older ( $n = 25$ ) to the patients who died before 10 years of age ( $n = 6$ ), we saw an overrepresentation of congenital heart defects and GERD in the deceased patients (Table 2). In a previous study, these features were found in 4/5 and 2/5 deceased patients, respectively (17). Congenital heart defects can lead to post-neonatal death due to rhythm disturbances and circulatory standstill. However, in patients with no prior history of rhythm disturbances, this is not a common cause of death. The other risk factors, feeding difficulties and GERD, both pre-dispose to respiratory aspiration, which can lead to premature death. Both are seen in the majority of CHARGE patients (8, 17, 22–24). Respiratory aspiration is also common in CHARGE syndrome (prevalence 47–74%) (17, 22, 25). This explains why the combination of feeding/breathing problems and GERD

have been determined as risk factors for premature death in our study group.

CN dysfunction is prevalent in CHARGE syndrome and is likely to be the underlying common risk factor, as it can cause both swallowing/breathing problems and GERD. CN V, VII, IX, X and XII play an important role in the swallowing process, as they coordinate muscle movements and supply sensory information from the oral, pharyngeal and laryngeal region (Table 3) (24, 26). Blake et al. reported dysfunction of at least one CN in 92% of patients with CHARGE syndrome and described multiple CN involvement in 72% (5). The underlying cause of CN dysfunction in CHARGE syndrome is unknown, but abnormalities of the brainstem or CN nuclei could play a role. Unfortunately, hardly any research has been performed by MRI brain imaging or by post-mortem brain examination, to unravel the anatomical substrates underlying the CN anomalies in CHARGE syndrome. Detailed clinical assessment of CN function in CHARGE syndrome patients may also shed light upon the precise role of CN dysfunction in swallowing, aspiration, GERD and other possibly fatal complications.

In order to prevent premature death in patients with CHARGE syndrome, we recommend that every CHARGE patient with feeding difficulties (at present or in the past) should be thoroughly assessed by a multidisciplinary team (preferably consisting of an ear-nose-throat (ENT) surgeon, gastroenterologist, physiotherapist, occupational therapist, speech therapist, and nutritionist). CN function should be investigated and should include analysis of chewing/biting (V), facial muscles (VII), velum function (IX), larynx mobility and closure of glottis (X), gag and cough reflexes (IX/X), tongue movement (XII), and the assessment of sensibility of the oropharynx (V, VII), pharynx (IX) and larynx (X). Swallowing studies, laryngopharyngoscopy, esophageal pH studies, esophageal manometry, and polysomnography may also be appropriate (27). In order to prevent respiratory aspiration, swallowing problems and GERD should be treated without delay. Possible treatments include gastrostomy, anti-reflux medication, and fundoplication. Respiratory problems can necessitate tracheotomy, but sometimes injection of botulinum toxin (botox) into the salivary glands can avert this (5, 28). In patients with a high risk of choking (as evaluated by the multidisciplinary team), we advise training the family or home carers in cardiopulmonary resuscitation, and the Heimlich maneuver. For all patients with CHARGE syndrome, careful pre-operative assessment is also important and surgical procedures

Table 3. Overview of cranial nerve involvement in phases of normal swallowing

Swallowing phase	Action	I/V	Cranial nerves	
			Motor	Sensory
Oral phase	Mastication of the food and mixing it with saliva for passage into the oropharynx	V	V3, VII, XII	V, VII, IX
Pharyngeal phase	Swallow reflex: soft palate moves upward, larynx and hyoid bone move forward and upward, epiglottis folds back, tongue pushes food bolus into the hypopharynx	I	V3, VII, IX, X, XII	IX, X
Esophageal phase	Downward movement of food bolus by a peristaltic wave from the upper to the lower esophageal sphincter, entrance of food bolus into the stomach	I	X	X

I, involuntary; V, voluntary; V3, mandibular branch of trigeminal nerve; VII, facial nerve; IX, glossopharyngeal nerve; X, vagus nerve; XII, hypoglossal nerve.

should be combined whenever possible. In addition, a pediatric anesthesiologist and/or laryngologist should be present in the operating room to anticipate possible intubation problems. Patients with CHARGE syndrome should be monitored for longer after surgery in order to identify and treat post-operative airway events. Finally, we strongly advise to perform autopsy in deceased CHARGE patients in order to gain more insight into causes of death.

In conclusion, post-neonatal death is not a rare event in patients with CHARGE syndrome and it often occurs unexpectedly. Gastro-esophageal reflux and poor coordination of swallowing and breathing due to CN dysfunction seem to be the major risk factors.

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