

Cranial Nerve Manifestations in CHARGE Syndrome

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Cranial nerve (CN) anomalies have been regarded as a major criterion for a clinical diagnosis of CHARGE syndrome for some time. However, there have been relatively few studies of the extent of this involvement. A detailed questionnaire (in French or English) was distributed to all physicians who participated in the 2001–2004 Canadian Paediatric Surveillance Program (CPSP), and who identified themselves as caring for an individual with CHARGE syndrome. Clinical data were collected from multiple sources for each individual, including evidence of CN dysfunction. Evidence for CN anomalies recorded by the clinical presentations and evidence from specialized testing, were: weak chewing and/or sucking (CN V), facial palsy (CN VII), sensorineural hearing loss (CN VIII), balance vestibular problems (CN VIII), and swallowing problems (CN IX/X). Data were analyzed as to the frequency of the CN anomalies and

compared to the literature. At the time of this study, there were 99 individuals identified with CHARGE syndrome across Canada. The CHARGE syndrome diagnosis was confirmed by geneticists across the country. Gene testing was not available at the time of this study. Of these 92% exhibited symptoms of at least one CN anomaly, and 72% reported involvement of more than one. Isolated CN involvement was rare. Ascertainment was highest for CN IX/X, and lowest for VIII vestibular. The frequency of CN involvement was generally higher than that reported in the literature.

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Key words: CHARGE syndrome; cranial nerves (CNs); surveillance; sensorineural hearing loss; facial palsy; swallowing dysfunction

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INTRODUCTION

CHARGE syndrome was first identified by Hall [1979], and the acronym was applied in 1981 by Pagon et al. based on what seemed to be the most defining characteristics. However, with time, four anomalies emerged as key diagnostic indicators, as they are relatively common in CHARGE and uncommon in other syndromes [Blake et al., 1998]: coloboma, choanal atresia, characteristic CHARGE ear, and cranial nerve (CN) dysfunction. Several authors have suggested adding a fifth criterion of temporal bone anomalies [Amiel et al., 2001; Verloes, 2005]. Recently, mutations in or of the *CHD7* gene have been established as one cause of CHARGE [Vissers et al., 2004]. The mutations are largely stop mutations, resulting in a premature stop of the transcription of the gene and a truncated *CHD7* protein. This protein might be either non-functional or might not be transported. Since the *CHD7* gene regulates the expression of other genes, the effect can be quite variable. Because the *CHD7* mutations have been found in 60–65% of patients [Jongmans

et al., 2006; Lalani et al., 2006], diagnosis still relies on clinical features.

Interactions between the epithelium and the mesenchyme mediate crucial aspects of normal development. Williams [2005] proposed that CHARGE is due to a generalized disruption of mesenchymal–epithelial interaction. This theory is consistent with the finding of CN abnormalities. Traboulsi [2004] supports the abnormalities of sensory and motor CN nuclei in many rare syndromes which involve CN dysfunction. Although not specifically mentioning CHARGE syndrome, there are reports in the paper consistent with the patients having a diagnosis of CHARGE.

CN abnormalities have been reported in several studies. Byerly and Pauli [1993] reviewed the literature through 1991 and, along with records from

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their clinic, examined CN problems in 163 patients. Clinical signs or symptoms of CN dysfunction were frequently reported for CN VII, VIII, and IX and/or X, and infrequently reported for CN III and VI. Tellier et al. [1998] reported that 78% of 47 patients showed dysfunction of at least one CN, most commonly VIII (48%) and VII (36%).

This article reviews the frequency and type of CN manifestations in a Canadian population through a surveillance system. Specifically, this study reports on the prevalence of abnormalities of CN V, VII, VIII, and IX/X.

Cranial Nerve V

CN V innervates the muscles of mastication (chewing) and sensory regions of the face. While many children with CHARGE are known to have dysphagia, chewing and sucking have not been studied. Strömland et al. [2005] report that 18 of 31 children with CHARGE had chewing and swallowing problems, but they did not distinguish between the two problems.

Cranial Nerve VII

CN VII controls the muscles of facial expression and also innervates the salivary and lacrimal glands. Byerly and Pauli [1993] found 70 of 163 patients to have facial palsy or functional facial asymmetry, suggesting CN VII involvement. Tellier et al. [1998] reported that 17 of 47 patients had facial palsy. Blake et al. [1990] reported facial palsy in 21 of 50 patients. Edwards et al. [1995, 2002] reported on two cohorts of children, one from 1983 to 1993, and the other 1994–2000. Of the 41 patients included in the two studies where data existed, 20 had facial palsy. More recently, in a Swedish study, Strömland et al. [2005] found 10 patients with facial palsy out of 31 patients. Seventy-seven parents of 160 children with CHARGE (48%) in a study by Hartshorne et al. [2005] reported their child had facial palsy. The authors have also noted that increased salivation is sometimes found with CHARGE, which would be consistent with an anomalous CN VII.

Cranial Nerve VIII

Williams [2005] points out that vestibular problems and sensorineural hearing loss may both be the result of abnormal development of the labyrinth. While there are many cases of successful cochlear implants in individuals with CHARGE [Bauer et al., 2002], there are also incidents where the auditory nerve cannot be fired or even found, and implantation does not take place.

In the literature, CN VIII anomaly has been most often inferred from sensorineural hearing loss, although Byerly and Pauli [1993] point out that not

all cases may necessarily mean CN VIII involvement. They found 98 of 163 patients with sensorineural or mixed hearing loss, the largest category of possible CN involvement they identified. Blake et al. [1990] found 34 of 50 to have sensorineural or mixed loss. Combining the two studies by Edwards et al. [1995, 2002], 22 of the 41 patients had either sensorineural or mixed loss. Tellier et al. [1998] indicated that 23 of their 47 patients had CN VIII involvement, although they did not specify the criteria they used.

CN VIII is also involved with equilibrium and balance. Hartshorne et al. [2005] reported that 80% of the parents of 160 children with CHARGE indicated their child had vestibular difficulties. Abadie et al. [2000] found vestibular dysfunction in all 17 of the children they examined.

Cranial Nerves IX and X

CN IX and X are both involved with swallowing which, as was pointed out above, is a common problem in CHARGE. Blake et al. [1998] claim that these difficulties appear to be due to CN involvement. Hartshorne et al. [2005] reported that 79% of 160 children had swallowing difficulties based on parent report.

Byerly and Pauli [1993] found 51 of the 163 children they reviewed to have swallowing difficulties that appeared to stem from CN involvement. However, they note that it is hard to delineate whether the dysfunction is due to the glossopharyngeal and/or the vagus nerves. Either or both could account for the feeding problems, abnormal swallow, and dependence on gastrostomy. They also pointed out that feeding problems can be due to causes other than CN dysfunction, and so their data should be considered estimates only.

MATERIALS AND METHODS

A standardized questionnaire survey (in French and English) completed by physicians concerning individuals with CHARGE syndrome was conducted through the Canadian Paediatric Surveillance Program (CPSP) from September 2001 to August 2004 (preliminary results and study design can be found in Issekutz et al. [2005]). The physicians across Canada who identified the individuals with CHARGE were asked to complete an extensive reporting form incorporating the multiple CHARGE features, as well as assessments from therapists involved in the individuals' care and demographic data. Five features indicative of CN anomalies were recorded for each patient. These included weak chewing/sucking (CN V), facial palsy (CN VII), sensory-neural deafness (CN VIII), balance/vestibular problems (CN VIII), and swallowing problems (CN IX/X). Physicians could also indicate that the information was not available. The data could have been collected from

multiple sites as this population would often see numerous clinicians and therapists [Blake et al., 1990].

The data were analyzed for the frequency of these anomalies and certain relationships and trends between them. In addition, the review of the literature was used in order to make a comparison of these CN anomalies with a larger CHARGE population and to draw on speculations in pathogenesis [Williams, 2005].

The diagnosis of CHARGE was made using the clinical criteria developed by Blake et al. [1998], using the four major criteria (choanal atresia, coloboma, characteristic CHARGE ear, CN dysfunction) and seven minor criteria (genital hypoplasia, developmental delay, cardiovascular malformations, growth deficiencies, orofacial cleft, tracheoesophageal-fistula, characteristic face). At the time of this study gene testing for the *CHD7* mutation was not available.

Inclusion Criteria

The diagnosis could be based on the presence of all four major criteria, three major and three minor, or a previous diagnosis that included a combination of major and minor plus some occasional findings (renal, hand, spine/limb, abdominal (hernia) abnormalities).

Exclusion Criteria

Other conditions, such as velocardiofacial syndrome (VCS) and DiGeorge Sequence (DGS) using the FISH test (Fluorescent In Situ Hybridization) to exclude 22q11 deletion, were exclusion criteria.

RESULTS

At the time of this survey, there were 99 individuals across Canada clinically identified with CHARGE syndrome. A description of a portion of this group and findings is given by Issekutz et al. [2005]. Physicians reported the presence of CN anomalies as described in methodology and, if present, specified weak chewing/sucking (CN V), facial palsy (CN VII), sensorineural deafness (CN VIII A), balance/vestibular problems (CN VIII), and swallowing problems (CN IX/X). Physicians specified whether the CN was affected or not, or whether they did not have enough information available to make that determination. If the patient was deceased at an early age there may have been limited data. The older population often had extensive information from numerous sources to help with accurate data collection.

Of this group, 89 (92%) exhibited symptoms of at least one CN anomaly, although for one individual the specific CN affected was not specified. In addition, 71 (72%) reported involvement of more

than one CN. Figure 1 shows the percentage of CN involvement, non-involvement, and unknown for each of the specific CNs. CN VIII vestibular had the lowest ascertainment with only 22.2% identified and 60.6% unknown. CN VIII auditory was much more frequently identified with only 29% unknown. Overall, CN IX/X had the highest ascertainment. While CN VII had the lowest percent identified (45%), there were also not many unknowns. The right side of the face was more often involved than the left (31–18%), while 3% were reported to have bilateral facial palsy. CN V, which has not been studied in CHARGE, was ascertained in 55.6% of the children.

The CN findings from our cohort can be compared with those from the literature reviewed (the parent report from Hartshorne et al. [2005], was excluded) as shown in Table I. The frequency for CN VII was quite similar across studies. However, for CN VIII auditory and CN IX/X, the present study found a much higher frequency than had been reported previously. For CN VIII vestibular our finding is lower than that of Abadie et al. [2000]; however, her findings are based on MRI studies and may reflect structural as opposed to neural anomalies.

Combinations of CN anomalies for the 88 individuals with at least one CN abnormality were examined. For this analysis, the two kinds of CN VIII anomalies were combined because they reflect the same nerve. Isolated CN anomalies were rare with the exception of CN VIII (Table II). CN VIII also appeared in a number of dyads and triads. Sixteen individuals had all four CN anomalies. The finding that the CN anomalies frequently co-occur supports Williams' [2005] theory of the pathogenesis of CHARGE.

DISCUSSION

CN involvement has long been identified as occurring in CHARGE, and is now considered one of the major criteria for a clinical diagnosis. This study of 99 individuals with CHARGE syndrome in Canada found that physician reported CN involvement had a higher occurrence than noted in previous studies. That so many of the individuals had all four reported CN anomalies (V, VII, VIII, IX/X) is particularly noteworthy, and may also be important for clinical management.

There were differences among the nerves in the apparent ability of the physicians to ascertain anomalies. For CN VIII vestibular, ascertainment was evidently very difficult, as anomalies were identified in fewer than one quarter, and nearly two-thirds were unknown. While a number of children with CHARGE do receive MRI neurological scans, these generally do not include a scan of the inner ear area unless specifically requested, and so vestibular anomalies are generally detected by the

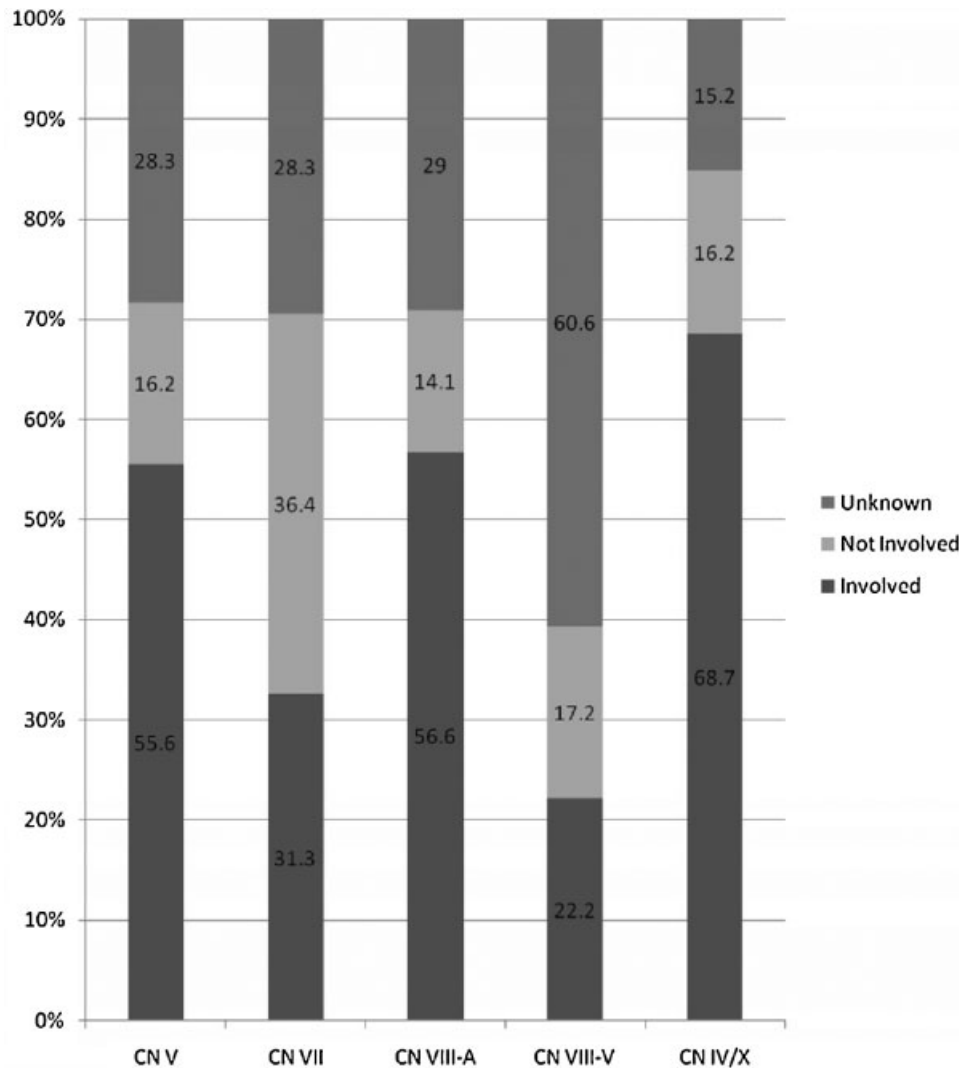


FIG. 1. Reported cranial nerve involvement.

motor difficulties these children demonstrate when they begin to try and walk [Williams and Hartshorne, 2005]. CN VIII auditory was much more easily identified with less than a third unknown. Because deafness is very prevalent in CHARGE, most children are given detailed audiometric tests. CN IX/X has the highest ascertainment, likely reflecting the widespread swallowing problems in CHARGE. While CN VII had the lowest percentage identified, there were also not many unknowns, as facial palsy is fairly easily identified. CN V was ascertained in more than half of the children. A weakness in the present study's design did not provide information regarding the means of ascertainment. Future studies, now that it is clear that CN involvement is a significant issue in CHARGE, should examine ascertainment methodology.

This is the first study to document involvement of CN V (weak chewing/sucking). While the prevalence of swallowing difficulties leading to gastro-

stomy and significant morbidity beyond the neonatal period [Blake et al., 1990; Dobbelsteyn et al., 2005] may be due to CN IX and X, the difficulty experienced by many children with CHARGE after they learn to eat with moving beyond pureed and blended food could be related to CN V. It is interesting that while most of the children are able to bite (objects/people), they have difficulty chewing food and coordinating that with a swallow. Maintaining oral stimulation for chewing and sucking during the years the child has a gastrostomy may be important for future normal eating. However, learning to chew and swallow because the nervous innervations may be disrupted will require more than oral stimulation. This brings into consideration other forms of therapy for the feeding team [Dobbelsteyn et al., in press].

The higher instances of CN involvement in CHARGE syndrome found in this study versus the research literature is of interest. Most of the literature is based on clinic samples although with

TABLE I. Frequency of CN Anomalies Reported in the Literature

	Study	Percent
CN VII		
Byerly and Pauli [1993]	70/163	43
Tellier et al. [1998]	17/47	36
Blake et al. [1990]	21/50	42
Edwards et al. [1995]	10/20	50
Edwards et al. [2002]	10/21	48
Strömmland et al. [2005]	10/31	32
Current study	31/67	46
CN VIII (cochlea)		
Byerly and Pauli [1993]	98/163	60
Tellier et al. [1998]	23/47	49
Blake et al. [1990, 1998, 2005]	34/50	68
Edwards et al. [1995]	9/21	43
Edwards et al. [2002]	12/21	57
Current study	56/70	80
CN VIII (vestibular)		
Abadie et al. [2000]	17/17	100
Current study	22/39	56
CN IX/X		
Byerly and Pauli [1993]	51/163	31
Current study	68/84	81

the identification of the *CHD7* mutation a broader population with milder features may be ascertained, and some are based on case histories that may or may not include information related to all CNs. Although CN involvement was suggested as a major diagnostic criterion for CHARGE in 1998, some physicians continue to rely on the acronym [Pagon et al., 1981] for diagnosis, and thus may not report, or may overlook evidence of, CN problems. They may in addition be uncertain how to ascertain some CN involvement. The physicians in this study did not specify how the CN anomalies were ascertained. There may be multiple methods of ascertainment, for

TABLE II. Frequencies of Combinations of Cranial Nerve Anomalies

Reported involvement	N	% Out of 88
Isolated		
CN V	3	3.4
CN VI	1	1.1
CN VIII	8	9.1
CN IX/X	6	6.8
Dyads		
V and VII	1	1.1
V and VIII	3	3.4
V and IX/X	14	15.9
VII and VIII	2	2.3
VII and IX/X	0	0
VIII and IX/X	10	11.4
Triads		
V, VII, and VIII	2	2.3
V, VII, and IX/X	3	3.4
V, VIII, and IX/X	13	14.7
VII, VIII, and IX/X	6	6.8
Tetrads		
V, VII, VIII, and IX/X	16	18.2

example, behavioral, physiological, radiographic, anatomical, and genetic. Multiple methods may need to be applied in order to rule out CN involvement. In the meantime, given the co-occurrence of the CNs in this study, it may be worthwhile looking for evidence of further CN anomalies.

The finding that multiple CNs tend to be affected suggests that as CHARGE is better understood, we may find that in some cases all 12 pairs of CNs can be involved, although there are no data at the present time to suggest this. Speculations by Williams [2005] on the pathogenesis of CHARGE syndrome support the involvement of CN V. As Williams notes, CN V, VII, IX, and X are different from other motor nerves because they have associated sensory ganglion, derived from the interaction of the neural crest mesenchyme and ectodermal placodes. The fact that CHARGE CN anomalies are seen in these nerves is likely due to the unique induction events that generate the sensory ganglia. More extensive testing for CN involvement, along with anticipating difficulties related to CN involvement should be standard care for individuals with CHARGE syndrome. In the following discussion we speculate about CN involvement in CHARGE with the aim to encourage additional research and clinical findings.

Cranial Nerve I

CN I mediates the sense of smell. Evidence for CN I involvement in CHARGE was found by Lin et al. [1990], who conducted a review of patients from the literature combined with eight new patients. Adequate information on the brains of 47 patients established central nervous system (CNS) malformations in 26 of them. Of these 11 showed arhinencephaly.

Byerly and Pauli [1993] found that 14 of their 163 patients had either absence or dysfunction of the olfactory tracts. They were unable to determine whether these were structural nervous system anomalies or true CN abnormalities.

Chalouhi et al. [2005] used a specific test for olfaction in children with a group of 14 with CHARGE and a control group of 25 healthy children. All of the children with CHARGE had olfactory deficit ranging from mild hyposmia to complete anosmia.

Cranial Nerves II, III, IV, and VI

Eye problems are common in CHARGE, including coloboma, microphthalmia, and eye tracking. Russell-Eggitt et al. [1990] found ocular abnormalities in 44 out of 50 patients with CHARGE. Of these, 41 had "typical" colobomata, the majority with retinochoroidal colobomata with optic nerve involvement, and 13 patients with an iris defect. Two patients had atypical iris colobomata with normal fundi. Additional features included microphthalmos in

21 patients, optic nerve hypoplasia in four, nystagmus in 12, and a vertical disorder of eye movement in 4 of the 22 patients with facial palsy. Detailed eye testing that might reflect problems with CN II, III, IV, and VI may be a challenge. Problems with eye tracking might also be attributed to those conditions and also to the problems with the vestibular system and CN VIII, therefore missing the other possible links. McMains et al.'s [2004] study undertook extensive ophthalmological (including electrodiagnostic and orthoptic) and functional vision testing in a small group ($n=8$) of individuals with CHARGE. These in-depth results obtained evidence of an extraocular motility defect of limited elevation in adduction due to isolated inferior oblique paresis in 44% of the patients.

Cranial Nerve V

As discussed in this article, CN V may be affected in varying degrees especially the motor axons that innervate the muscles of mastication and the sensory axons from the face and the cornea. CN V has also been implicated in migraine headaches [Hargreaves, 2007]. Migraine symptoms have been highlighted as adolescent concerns in CHARGE syndrome [Blake et al., 2005] as well as by informal parent report. Dodick and Silberstein [2006] describe the central sensitization hypothesis for migraines which links to "cutaneous allodynia," or pain arising from innocuous stimuli from the skin such as the touching of a fluffy toy. This kind of tactile defensiveness and sensitivity in CHARGE has been frequently reported by parents and is discussed by Brown [2005]. Other trigeminal autonomic headaches with pain and autonomic involvement in the area supplied by the trigeminal nerve [May, 2006] may prove to be a phenomenon in CHARGE given problems with CN V. Similar to the facial and vestibulocochlear nerve, the trigeminal nerve may be intact on one side and not the other. More investigation is clearly needed.

Cranial Nerve VII

CN VII had the lowest percent ascertained in our study, however there were also not many unknowns, as facial palsy is fairly easily identified. This nerve is well known to be involved in CHARGE syndrome however bilateral facial Paresis is more difficult to detect and may be under-diagnosed. The child with bilateral paresis can look disinterested and expressionless, leading to lowered expectations of others for the child [Brown, 2005]. CN VII also innervates the salivary and lacrimal glands. One of the authors (KB) has used Botox injections into the salivary glands to aid extubation in an infant who has excessive secretions in his oral cavity which was looking as if a tracheostomy would be the only choice. Six months later injections were repeated because of excessive

secretions and aspiration pneumonias. Aspiration of secretions from the upper airways have also been identified as a source of increased morbidity and mortality [Blake et al., 1990; Blake et al., 2007].

Cranial Nerve VIII

The vestibuloacoustic nerve has been well researched in CHARGE; however, the growing reports of the abnormalities of the temporal bone may add to this being one of the major clinical criteria for CHARGE. It is important that when imaging of the brain is completed an MRI is ordered which includes temporal bone cuts. This has not always been the case, and this may be one reason CN VIII had the lowest ascertainment of the nerves in the present study. Having a clinical diagnosis of vestibular anomaly may be important especially for the older population that may not require further imaging from a clinical standpoint.

Cranial Nerves XI and X

CN IX/X had the highest ascertainment in our study, likely reflecting the widespread swallowing problems found in CHARGE. The glossopharyngeal nerve innervates the pharynx and mediates the swallowing reflex. The Brachial Motor part of the vagus supplies the muscles of the pharynx and larynx. Although many researchers have implicated this nerve and the vagus (CN X) to be involved in CHARGE syndrome there still requires anatomical and functional proof to this statement. The adolescent and adult paper by Blake et al. [2005] makes reference to the "abdominal colic" that this population reports. This sensation clinically looks distinct from the gastroesophageal reflux symptoms of the upper gastrointestinal tract and may reflect the visceral sensory innervation of the vagus. The vagus nerve has been proposed as the primary neuroanatomic substrate of the gut-brain axis [Koren and Holmes, 2006].

Cranial Nerve XI

Many children with CHARGE experience shoulder and neck problems. Asymmetry of the appearance of the neck which is well reported by parents and evident in pictures may be the result of CN XI anomalies. Although the literature does not support kyphosis and scoliosis as a result of CN XI there is limited understanding of the cause of scoliosis in general which is more prevalent in the CHARGE population than was originally thought. A population of adolescents and adults studied by Blake et al. [2005] identified scoliosis as a highly prevalent clinical characteristic which Doyle and Blake [2005] further defined. One-third of the 160 parents in the study by Hartshorne et al. [2005]

reported spine anomalies in their child. These studies suggest a potential link with CN XI dysfunction.

Cranial Nerve XII

Tongue problems have also been anecdotally noted in CHARGE, suggesting a possible link to CN XII. While this has not been reported in the literature, given the complications associated with the other CNs, this is an area that should be investigated.

Limitations and Future Directions

As a cross sectional population based study, these results depend on the accuracy of the reporting physician. In addition, the reporting physicians were not necessarily specialized in neurological evaluation. In fact, the particular expertise of the reporting physicians was not standardized; however, there was substantial input from numerous clinicians and therapists who added to the clinical descriptions of this population and helped define the anomalies. MRI examinations were limited and not always completed to look at the temporal bones and olfactory tracts. More clinical studies around testing for specific CN dysfunction, such as Chalouhi et al. [2005] are needed. Especially needed is more investigation of CN V and IX/X to support Williams [2005] hypothesis.

The diagnosis of CHARGE in these patients was clinical because the *CHD7* gene anomalies had not yet been reported. However, this population is at present being gradually tested with similar positive *CHD7* mutation results to the published literature. Studies show that the clinical criteria that have been used are highly specific for the gene mutation [Lalani et al., 2006]. It is possible that those children with a clinical diagnosis of CHARGE but not the *CHD7* gene mutation might have a different CN profile from those with the gene mutation. As well the mild variation of CHARGE syndrome patients who are *CHD7* positive and have fewer clinical criteria may also show a variation in their CN profile.

Future research should seek to identify additional possible CN links in CHARGE. Studies should include detailed brain imaging for all individuals with CHARGE. An examination of the relationship between the structural malformations and the clinical symptoms of CN dysfunction could provide important etiological information. Further objective, detailed, neurological studies are needed to evaluate the abnormal CNs in CHARGE syndrome and so localize the specific defects. More population-based studies are called for to clarify the typical rate of CN involvement in CHARGE.

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