Received: 12 September 2019 | Revised: 6 November 2019 | Accepted: 17 December 2019

DOI: 10.1002/lio2.343

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

Prevalence and significance of cranial nerve imaging abnormalities in patients with hereditary neuropathies: Clinical implications at the skull base

Ryan A. Bartholomew MD[1] | Amir A. Zamani MD[2] | Grace S. Kim MD[3] | Jennifer C. Alyono MD[3] | Haley Steinert BA[4] | Vera Fridman MD[4] | Reza Sadjadi MD[5] | Robert K. Jackler MD[3] | C. Eduardo Corrales MD[1]

[1]Division of Otolaryngology-Head and Neck Surgery, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts

[2]Division of Neuroradiology, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts

[3]Department of Otolaryngology-Head and Neck Surgery, Division of Otology & Neurotology, Stanford, Stanford University School of Medicine, California

[4]Department of Neurology, University of Colorado School of Medicine, Aurora, Colorado

[5]Department of Neurology, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts

Correspondence
C. Eduardo Corrales, MD, Division of Otolaryngology—Head and Neck Surgery, Harvard Medical School, Brigham and Women's Hospital, 45 Francis Street, Boston, MA 02115.
Email: ccorrales@bwh.harvard.edu

Abstract

Objective: To estimate the prevalence and significance of cranial nerve (CN) imaging abnormalities in patients with hereditary neuropathy and discuss clinical implications.

Methods: We retrospectively analyzed data from patients at four tertiary academic medical centers with hereditary neuropathy diagnoses who had undergone gadolinium-enhanced magnetic resonance imaging (MRI) of the brain or skull base between 2004 and 2018. MRI scans, as well as computed tomography imaging when available, were reviewed and bivariable analysis was performed to identify predictors of CN abnormalities on imaging.

Results: Among 39 patients meeting study criteria, 11 had clinical CN deficits (28%) and 8 had CN abnormalities on imaging (21%). Of the patients with CN abnormalities on imaging, half had CN deficits (4/8) and only a quarter had imaging abnormalities of the CNs with the deficits (2/8). Imaging abnormalities were found in varied CNs, including CNs III, V, VII, and the VII/VIII complex in the internal auditory canal. MRI obtained for the purpose of evaluating CN deficits had a statistically significant increased likelihood of containing CN imaging abnormalities. However, CN deficits themselves were not predictive of imaging abnormalities.

Conclusion: Thickening and enhancement of CNs on MRI may be found in approximately 1/5 of patients with hereditary neuropathies and are inconsistently associated with clinical deficits. These imaging findings should not be mistaken for neoplastic and infectious processes as they may be manifestations of the patients' underlying genetic neuropathy.

Level of Evidence: 4.

KEYWORDS

Charcot Marie Tooth, cranial nerves, hereditary motor and sensory neuropathy, hereditary neuropathy, MRI, skull base

TABLE 1 Summary of hereditary neuropathy patient case reports with CN imaging abnormalities

	Diagnosis	Neuropathy phenotype	CN deficits	Imaging findings
Das, 2017[2] (27F)	HMSN 1A	Chronic, progressive sensorimotor deficits of the bilateral lower extremities.	Tinnitus	MRI: Thickening and enhancement of bilateral trigeminal and facial nerves CT: Bilateral enlargement of foramina rotundum and ovale
Frisch, 2017[3] (49M)	HMSN (unspecified type)	Subclinical evidence of peripheral demyelination on nerve conduction studies	Left facial paresthesia, left conductive hearing loss due to antral obstruction and ossicular chain contact by an enlarged facial nerve	Brain MRI: Thickening of bilateral cisternal trigeminal and facial nerves. Mild left cisternal trigeminal nerve enhancement CT: Bilateral thickening of facial nerves with abutment of the ossicular chain
Shizuka, 1999[4] (15F)	HMSN 1B	Chronic, progressive sensorimotor deficits	No clinical deficits Auditory brainstem response: prolongation of the I-III interpeak intervals suggesting peripheral conduction delay of auditory nerve	MRI: Bilateral thickening of cisternal trigeminal nerves
Mitsui, 1994[5] (15F)	HMSN 1B	Chronic, progressive sensorimotor deficits	None	MRI: Bilateral thickening of cochlear nerves
L'Heureux-Lebeau, 2013[6] (28F)	HMSN (unspecified type)	None reported	Bilateral conductive hearing loss and absent acoustic reflexes	MRI: Bilateral thickening of the trigeminal, facial, and glossopharyngeal nerves. CT: Bilateral facial nerve enlargement with ossicular erosion and filling of round window niche
Ito, 1998[7] (36M)	HMSN 1A	Chronic, progressive sensorimotor deficits	Delayed latency of blink reflex and prolongation of facial nerve latency on nerve conduction studies	No reported imaging
Aho, 2004[8] (64M)	HMSN 1A	Chronic, progressive sensorimotor deficits	Bilateral deafness and right facial pain diagnosed as trigeminal neuralgia	MRI: Bilateral thickening and faint enhancement of cisternal oculomotor nerves, V2 and V3 trigeminal nerve segments, and mastoid facial nerve segments CT: Bilateral enlargement of foramen rotundum, ovale, and mastoid facial nerve canals
Saito, 1993[9] (53M)	HMSN 1	Chronic, progressive sensorimotor deficits. Positive pyramidal tract signs.	Bilateral progressive sensorineural hearing loss and vision loss	MRI: No CN abnormalities
Kulkarni, 2015[10] (14M)	HMSN 1A	Chronic, progressive sensorimotor deficits	Abnormal constriction and elevation of right palatal arch, deviation of the uvula to the left, right hemiatrophy of the tongue	MRI: No CN abnormalities
Pareyson, 2000[11] (67M, 33F)	HMSN 1 (EGR2 mutation)	Father and daughter with chronic, progressive sensorimotor deficits	Father: progressive diplopia consistent with left oculomotor nerve palsy, bilateral hearing loss,	MRI: no CN abnormalities

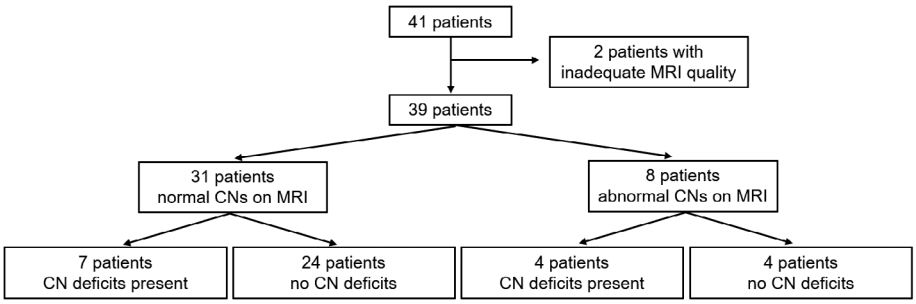
(Continues)

TABLE 1 (Continued)

Diagnosis	Neuropathy phenotype	CN deficits	Imaging findings
		bilateral vocal cord palsy requiring tracheostomy Daughter: no clinical CN deficits Both had reduced amplitudes and prolonged latencies on compound muscle action potential testing of the facial and spinal accessory nerves.	

Note: Patient age in years and sex in parentheses on left.
Abbreviations: CN, cranial nerve, CT, computed tomography, HMSN, hereditary motor and sensory neuropathy; MRI, magnetic resonance imaging.

FIGURE 1 Flow chart demonstrating number of patients analyzed



1 | INTRODUCTION

Hereditary neuropathy, also referred to as Charcot-Marie-Tooth disease, encompasses a heterogeneous group of rare genetic conditions characterized by motor and sensory deficits in the extremities, the most common of which is the hereditary motor and sensory neuropathy (HMSN) group of conditions. The HMSN disease processes preferentially impact the larger and longer neuronal fibers of the extremities.[1] Cranial nerve (CN) involvement can occur, clinically or radiographically, but is less frequently reported.[2-11]

Implicated mutations in these conditions typically disrupt the formation and maintenance of axonal myelination and integrity.[1] HMSNs are frequently classified according to their appearance on peripheral nerve biopsy and by their properties on nerve conduction studies.[1] HMSN1 is characterized predominantly by axonal demyelination and can have features of nerve hypertrophy on peripheral nerve biopsy. HMSN2 is characterized predominantly by axonal degeneration and rarely hypertrophy on peripheral nerve biopsy. Other types of HMSN are characterized by mixed features on peripheral nerve biopsy. More importantly, diagnosis is often made based off of the patient's clinical phenotype, with family history, peripheral nerve biopsy, nerve conduction studies, and genetic testing being used to further refine the diagnosis.[1]

Pathologic involvement of CNs on imaging in patients with hereditary neuropathy is limited to case reports (Table 1).[2-8] Described abnormalities on magnetic resonance imaging (MRI) include smooth thickening, mild enhancement with gadolinium, or both of varied CNs.[2-7] Computed tomography (CT) has identified enlargement of skull base foramina.[2,3,8] Imaging abnormalities have been identified in patients with[3,8] and without[2,4-6] attributable symptoms. Even among the reported patients with CN deficits, many of the abnormally appearing CNs were asymptomatic. Moreover, CN deficits also occur in the absence of imaging abnormalities.[7,9-11] The progression and persistence of imaging abnormalities in these patients are not known.

CN imaging abnormalities in patients with hereditary neuropathy share many features with neoplastic and infectious pathologies which may require targeted management by otolaryngologists and skull base surgeons. In other contexts, these imaging abnormalities could suggest perineural spread of a head and neck cancer, leptomeningeal spread of an intracranial malignancy, schwannomas of the skull base, or an infectious process.[12] The aim of our multicenter study was to further characterize the prevalence and significance of CN imaging abnormalities in patients with hereditary neuropathies who undergo MRI. We analyzed the appearance of CNs on gadolinium-enhanced MRI brain or skull base scans from patients with hereditary neuropathy. When available, CT imaging was also reviewed. Patient demographics and clinical data, including CN deficits, were investigated to ascertain associations with imaging abnormalities.

2 | METHODS

2.1 | Patients

Because no one health center has enough patients with hereditary neuropathy to allow for meaningful analysis, we partnered with

TABLE 2 Patient demographics, disease characteristics, and imaging characteristics

Variable	Quantity or mean (frequency %), N = 39	Bivariable comparison of CN abnormalities on MRI by given variable: *P* value
Age (years)	48.9	.42
Abnormalities on imaging	43.5	
No abnormalities on imaging	50.3	
Sex		1.00
Male	20 (51)	
Female	19 (49)	
HMSN diagnosis		NA
HMSN (unspecified type)	18 (46)	
HNPP	4 (10)	
HMSN1	12 (31)	
HMSN2	4 (10)	
HMSN5	1 (3)	
Neuropathy pathology		NA
Unspecified	18 (46)	
Demyelinating	16 (41)	
Axonal	5 (13)	
Intermediate	0	
MRI protocol		.10
Brain MRI	36 (92)	
Dedicated skull base MRI	3 (8)	
CN abnormalities on MRI[a]	8 (21)	NA
Type of abnormalities		
CN thickening only	3	
CN enhancement only	1	
Both	4	
Symmetry of abnormalities		
Symmetric abnormalities	4	
Asymmetric abnormalities	4	
CNs Involved (unilateral or bilateral)		
CN III	1	
CN V	5	
CN VII (distal to the IAC)	5	
CN VII/VIII complex in the IAC	4	
CN deficits	11 (28)	.19
Concurrent CN abnormalities on MRI		
Any CN(s)	4	
Corresponding CN(s)	2	
Indication for MRI		**0.01**
CN deficit	6 (15)	
Other	33 (85)	
CT available	15 (39)	.69
CN foramina enlargement	4	

Note: Bold indicated statistical significance.
Abbreviations: CN, cranial nerve; CT, computed tomography; HMSN, hereditary motor and sensory neuropathy; IAC, internal auditory canal; MRI, magnetic resonance imaging.
[a]Refer to Table 3 for greater characterization of patients with CN imaging abnormalities.

four major academic centers to gather enough patients for the study. The Brigham and Women's Hospital, Massachusetts General Hospital, Stanford Medical Center, and University of Colorado School of Medicine institutional review boards approved the study. Through electronic medical record databases at these tertiary care referral centers, patients with a hereditary neuropathy diagnosis who had undergone a gadolinium-enhanced MRI of the brain or skull base between 2004 and 2018 were retrospectively identified. Broad search terms were used to ensure capture of alternative names used for hereditary peripheral neuropathy. These included "hereditary peripheral neuropathy", "HMSN", "Charcot Marie Tooth", "CMT", and "peroneal muscular atrophy." All patients had been diagnosed by a neurologist using available clinical phenotype, family history, biopsy, nerve conduction, and genotype data. Inclusion criteria for MRI scans were presence of T1-weighted sequences with and without gadolinium, visualization of the skull base, and minimal motion artifact. Collected patient data included gender, hereditary neuropathy diagnosis, age at time of MRI, imaging indication, and signs and symptoms suggestive of CN deficits.

2.2 | Imaging

MRI sequences were reviewed using axial, coronal, and sagittal planes. CN abnormalities, including enhancement and thickening, were noted. When available, CT scans of the head were reviewed for enlargement of CN foramina. Review of imaging was conducted by physicians trained in either neuroradiology or skull base surgery. Each scan was analyzed independently by two reviewers who were blinded to patient name, demographics, and clinical history. Marginal findings were called abnormal only when they were corroborated by findings on successive slices and alternative planes or by corresponding CN foramina enlargement on CT (when available).

TABLE 3 Summary of patients with cranial nerve imaging abnormalities

	Hereditary neuropathy diagnosis	Neuropathy phenotype	Cranial nerve deficits	Imaging findings
Patient 1 (45M)	HMSN (unspecified type)	Chronic, progressive sensorimotor deficits of the bilateral extremities (upper>lower)	Tongue numbness and weakness	Brain MRI: Thickening of the left V3 trigeminal nerve CT: Not available
Patient 2 (31F)	HNPP	Bilateral upper and lower extremity paresthesias	None	Brain MRI: Enhancement of the left IAC fundus with a corresponding filling defect at the fundus on the T2-weighted sequence suggestive of nerve thickening CT: Not available
Patient 3 (75M)	HMSN (unspecified type)	Chronic, progressive sensorimotor deficits leading to wheelchair dependence	None	Brain MRI: Enhancement of the right IAC; thickening of the mastoid segment facial nerves bilaterally CT: Not available
Patient 4 (44M)	HNPP	Chronic, progressive sensorimotor deficits	None	Brain MRI: Bilateral thickening of cisternal trigeminal nerve on MRI; thickening of the right cisternal oculomotor nerve CT: Bilateral enlargement of the foramina rotundum and ovale
Patient 5 (63F)	HMSN (unspecified type)	Chronic, progressive sensorimotor deficits requiring bilateral ankle fusion	None	Brain MRI: Thickening and enhancement of the bilateral V2 trigeminal nerves and bilateral mastoid segment facial nerves. CT: Bilateral enlargement of the mastoid facial nerve canals. Unable to assess foramina rotundum due to unavailability of CT coronal view
Patient 6 (21M)	HMSN1 (INF2 mutation)	Chronic, progressive sensorimotor deficits; ESRD requiring kidney transplant and hearing loss thought to be related to INF2 mutation	Bilateral mild to profound sensorineural hearing loss and tinnitus	Skull base MRI: Bilateral enhancement and thickening of the IAC fundus; bilateral thickening of the cisternal, V2, and V3 trigeminal nerves and of the mastoid segment facial nerves CT: Bilateral enlargement of foramina rotundum, foramina ovale, and facial nerve canals (genu through the mastoid segment)
Patient 7 (52F)	HMSN (unspecified type)	Chronic, progressive sensorimotor deficits most significant for disequilibrium	Left tinnitus, bilateral mild sensorineural hearing loss (left > right)	Skull base MRI: Bilateral enhancement of the IAC fundus; bilateral enhancement of the facial nerve extending from the geniculate ganglion to the greater superficial petrosal nerve and tympanic segment of the facial nerve. CT: Not available
Patient 8 (18F)	HMSN (unspecified type)	Chronic, progressive sensorimotor deficits of the bilateral extremities (lower > upper)	Intermittent left eye diplopia and proptosis	Brain MRI: Bilateral thickening of V2 and V3 trigeminal nerves and mastoid segment facial nerves CT: Bilateral enlargement of foramina rotundum and ovale and mastoid facial nerve canals

Note: Patient age in years and sex in parentheses on left.
Abbreviations: EMG, Electromyography; ESRD, end stage renal disease; HMSN, hereditary motor and sensory neuropathy; HNPP, Hereditary Neuropathy with Liability to Pressure Palsy; IAC, internal auditory canal.

2.3 | Statistical Analysis

Descriptive analysis was performed to characterize patient demographics, clinical data, and imaging findings. Bivariable comparisons were performed using Student's t test for means and Fisher's exact tests for categorical variables. Alpha threshold for significance was tested at a level of 0.05. All statistical analyses were performed using JMP Pro v14 (SAS Institute, Cary, North Carolina).

3 | RESULTS

3.1 | Patients

A total of 41 patients were identified (Figure 1). Two patients were excluded due to inadequate imaging quality, leaving 39 patients remaining for analysis (Table 2). The mean patient age was 48.9 ± 24.1 years (range: 3-90 years) with a near equal proportion of males (20/39, 51%) and females (19/39, 49%). HMSN diagnoses were distributed among five categories: HMSN (unspecified type) (18, 46%), hereditary neuropathy with liability to pressure palsies (HNPP, 4/39, 10%), HMSN1 (12/39, 31%), HMSN2 (4/39, 10%), and HMSN5 (1/39, 3%). Conclusive genetic testing was available for 7 patients (18%), whereas the diagnoses for the remaining 32 (82%) of patients were made using available clinical phenotype, family history, biopsy, and nerve conduction data. CN deficits were documented in 11 patients (28%). Examples included facial and tongue paresis and/or paresthesia, sensorineural hearing loss, tinnitus, and diplopia (Table 3).

3.2 | Imaging characteristics

Most patients had MRIs protocolled for evaluation of the brain (36/39, 92%), with a minority having dedicated skull base MRIs (3/39, 8%) (Table 2). A minority of patients received an MRI for the indication of CN deficit evaluation (6/39, 15%). The imaging indications for the remaining patients were diverse and nonclustered. They included evaluation for stroke or multiple sclerosis (4/39, 10%), altered mental status (1/39, 3%), chiari malformation (1/39, 3%), nonglioblastoma intracranial mass (1/39, 3%), septic emboli (1/39, 3%), seizures (2/39, 5%), oncologic monitoring for brain metastases (2/39, 5%), Guillain-Barré syndrome (1/39, 3%), headache (5/39, 13%), central nervous system involvement of hereditary neuropathy (4/39, 10%), glioblastoma (5/39, 13%), developmental delay (2/39, 5%), deep brain stimulation for essential tremor (1/39, 3%), neurologic deficits out of proportion to known hereditary neuropathy (2/39, 5%), and unspecified (1/39, 3%).

The prevalence of patients with CN abnormalities on MRI in our cohort was 21% (8/39) (Table 3). Patients with abnormalities had CN thickening only (3/8), CN enhancement only (1/8), or both thickening and enhancement in the same or different CNs (4/8) (Figures 2 and 3). There was an equal distribution of patients with the same CNs abnormal bilaterally (symmetric, 4/8) and different CNs abnormal on the left vs the right (asymmetric, 4/8). Patients had imaging abnormalities in the following CNs, either unilaterally or bilaterally: CN III (1/8), CN V (5/8), CN VII distal to the internal auditory canal (IAC) (5/8), and the CN VII/VIII complex in the IAC (4/8). Half of the patients with imaging abnormalities had CN deficits (4/8), with only half of that subset having deficits that corresponded to at least some of the abnormally appearing CNs (2/8).

Fifteen patients in our cohort had CT imaging of the head (39%). Findings of CN foramina enlargement on CT which corresponded to CN thickening on MRI were found (Table 3). No patients underwent targeted intervention for CN abnormalities identified on imaging.

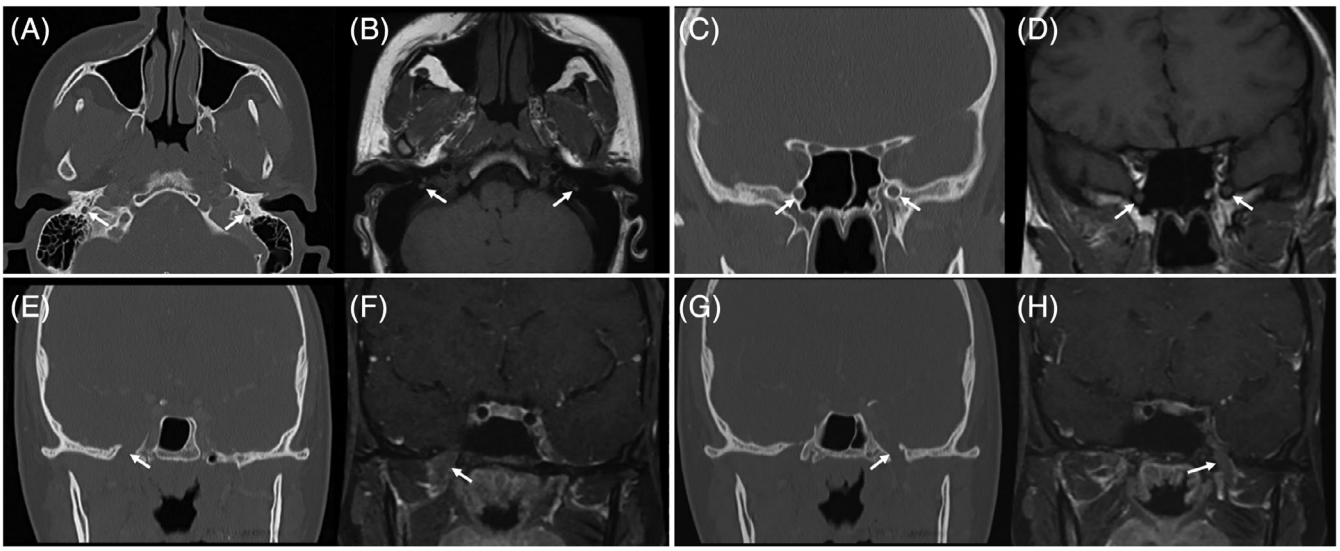


FIGURE 2 Cranial nerve thickening and foraminal enlargement. Patient 8: Bilateral mastoid facial nerve canal enlargement on axial view CT, A, with corresponding CN enlargement on axial view MRI, B. Bilateral foramen rotundum enlargement on coronal view CT, C, with corresponding CN enlargement on coronal view MRI, D. Bilateral foramen ovale enlargement on coronal view CT (right, E; left, G) with corresponding nerve enlargement on coronal view MRI (right, F; left, H). White arrows denote imaging abnormality. All MRI images are noncontrast T1-weighted sequences

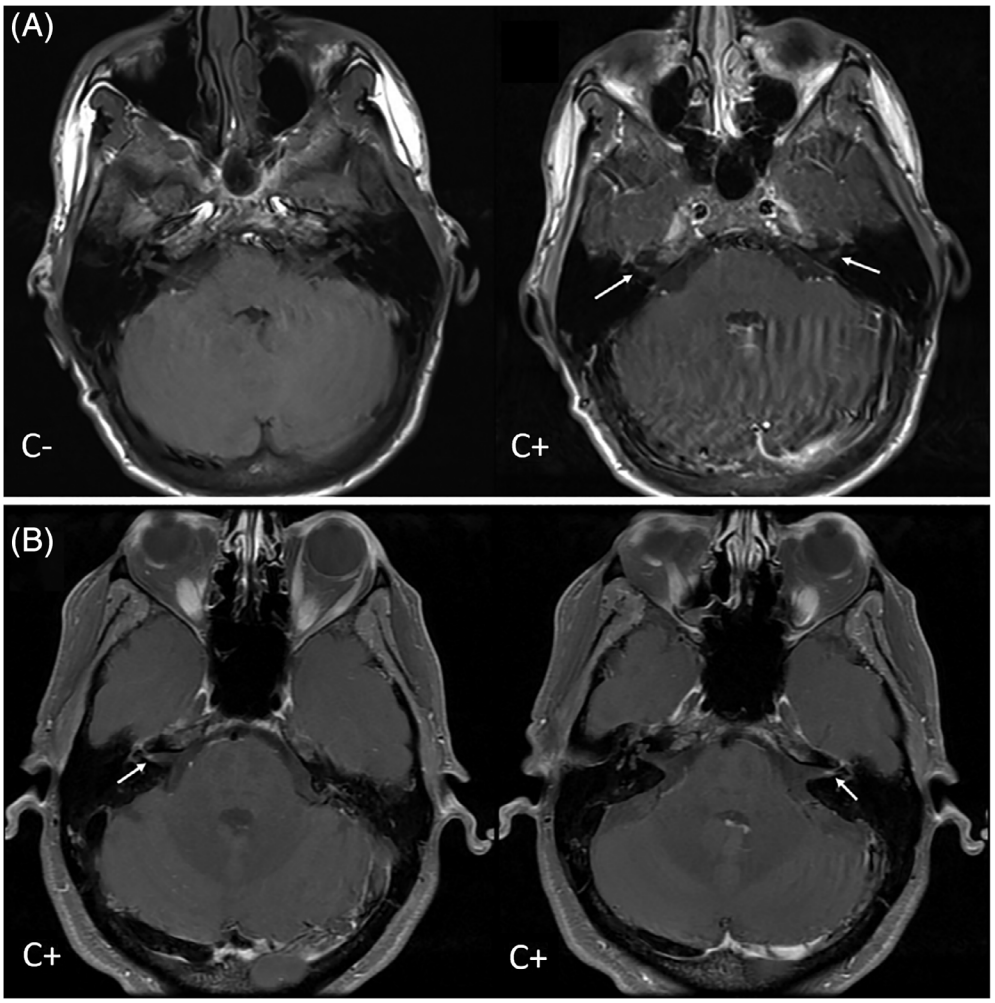


FIGURE 3 Abnormalities of the cranial nerve VII/VIII complex. A, Patient 6: T1-weighted gadolinium-enhanced MRI demonstrating bilateral fundal internal auditory canal enhancement and slight thickening in axial view (C+, on the right). Enhancement is not present prior to gadolinium administration (C–, on the left). B, Patient 7: Two consecutive T1-weighted gadolinium-enhanced MRI axial slices demonstrating bilateral fundal internal auditory canal enhancement. White arrows denote enhancement

3.3 | Predictors for CN abnormalities on MRI

Bivariable analyses were performed to identify factors associated with CN abnormalities on MRI (Table 2). CN abnormalities on MRI were not associated with patient age (abnormal MRI mean = 43.5 ± 19.6 years vs normal MRI mean = 50.3 ± 25.2 years, P = .42), sex (females 21.1% vs males 20.0%, P = 1.0), MRI protocol (brain 16.7% vs dedicated skull base 66.7%, P = .10), or the availability of CT imaging (available 26.7% vs not available 16.7%, P = 0.69). MRIs performed for the indication of CN deficit evaluation were more likely to be abnormal (CN deficit indication 66.7% vs other indication 12.1%, P = .01), although CN deficits themselves were not predictive of imaging abnormalities (CN deficits 36.4% vs no CN deficits 14.3%, P = .19). Sample size limitations precluded subgroup analyses of hereditary neuropathy type.

4 | DISCUSSION

A significant number of patients with hereditary neuropathy have CN abnormalities on MRI and CT scan as analyzed in this study. Many of these CN findings resemble pathologies requiring intervention by anterior and lateral skull base surgeons and thus warrant prudent observation as these abnormalities are likely inherent to the patients hereditary neuropathy. For example, IAC enhancement (Figure 3) often suggests vestibular schwannoma to the otolaryngologist, but in a patient with hereditary neuropathy it may be a manifestation of the patient's underlying disease process and therefore not require surgery or radiotherapy.

Whereas CN involvement on MRI has infrequently been described in hereditary neuropathy, we found a 21% prevalence of CN abnormalities in our cohort. Similar to prior case reports,[2-7] thickening and/or enhancement of varied CNs were identified. For patients with CN thickening on MRI, corresponding CN foramina enlargement was present on available CT imaging. CN pathology on imaging was inconsistently associated with clinical deficits—only two of the eight patients with imaging abnormalities had clinical deficits which could possibly be attributed to the abnormally appearing CNs. Moreover, while MRIs performed for the indication of CN deficit evaluation were positive predictors of imaging abnormalities, CN deficits were not.

Many challenges are inherent to evaluating CN imaging abnormalities in this patient population. The rarity of hereditary neuropathies, with an estimated prevalence of 0.04%,[13] makes the assembly of large cohorts difficult. This difficulty is further compounded by the limited

availability of these patients with brain or skull base MRIs. CN assessment was also limited by a paucity of dedicated thin slice imaging of the skull base, which may have limited our ability to identify subtle abnormalities. Moreover, care must be taken when applying conclusions drawn from our cohort of heterogenous hereditary neuropathies to any specific condition. One particular hypothesis for future studies is whether imaging abnormalities may occur more frequently in HMSN1, which is predominantly characterized by demyelination and can have features of nerve hypertrophy on peripheral nerve biopsy, than in HMSN2, which is predominantly characterized by axonal degeneration and rarely hypertrophy. Our study was unable to answer this question, with five of the patients with imaging abnormalities having an unspecified type of HMSN and the remaining three having either HMSN1 or HNPP (Table 3).

5 | CONCLUSION

Thickening and enhancement of CNs on MRI may be found in approximately 1/5 of patients with hereditary neuropathy who undergo MRI evaluation and are inconsistently associated with clinical deficits. These imaging abnormalities, which can mimic certain neoplastic and infectious processes, are unlikely to require targeted management and instead may be manifestations of the patient's underlying hereditary neuropathy. Thus, otolaryngologists, especially anterior and lateral skull base surgeons, should be aware of these inherent findings on imaging as one could erroneously diagnose an infection or neoplasm. That said, the authors recommend obtaining serial imaging for these patients on an annual basis, or when a change in clinic status occurs, to monitor for progression of imaging findings which may suggest a neoplastic, as opposed to a hereditary neuropathy, process. Spacing out the interval between serial imaging is reasonable after verification of the stability of the imaging findings.

ORCID

Ryan A. Bartholomew https://orcid.org/0000-0002-8310-3544
Reza Sadjadi https://orcid.org/0000-0003-3829-6030
Robert K. Jackler https://orcid.org/0000-0003-2525-8377

REFERENCES

1. Pareyson D, Marchesi C. Diagnosis, natural history, and management of Charcot-Marie-Tooth disease. *Lancet Neurol*. 2009;8(7):654-667.
2. Das N, Kandalaft S, Wu X, Malhotra A. Cranial nerve involvement in Charcot-Marie-Tooth disease. *J Clin Neurosci: Offi J Neurosurg Soc Aust*. 2017;37:59-62.
3. Frisch CD, Klein CJ, Carlson ML. Bilateral facial and trigeminal nerve hypertrophy in a patient with polyneuropathy. *Otol Neurotol: Offi Publ Am Otol Soc, Am Neurotol Soc [and] Eur Acad Otol Neurotol*. 2016;37(10):e404-e406.
4. Shizuka M, Ikeda Y, Watanabe M, et al. A novel mutation of the myelin P(o) gene segregating Charcot-Marie-Tooth disease type 1B manifesting as trigeminal nerve thickening. *J Neurol Neurosurg Psychiatry*. 1999;67(2):250-251.
5. Mitsui Y, Matsui T, Nakamura Y, Takahashi M, Yoshikawa H, Hayasaka K. A familial Charcot-Marie-Tooth disease type 1B (CMTD1B) manifesting a new mutation of myelin P0 gene. *Clin Neurol*. 1994;34(11):1162-1167.
6. L'Heureux-Lebeau B, Alzahrani M, Saliba I. Charcot-Marie-Tooth disease as a cause of conductive hearing loss. *Otol Neurotol: Offi Publ Am Otol Soc, Am Neurotol Soc [and] Eur Acad Otol Neurotol*. 2013;34(7):e105-e106.
7. Ito H, Tsuji T, Saito T, Kowa H, Harada H. Significance of facial and trigeminal nerve involvement in Charcot-Marie-Tooth disease type 1A: a case report. *Muscle Nerve*. 1998;21(8):1108-1110.
8. Aho TR, Wallace RC, Pitt AM, Sivakumar K. Charcot-Marie-Tooth disease: extensive cranial nerve involvement on CT and MR imaging. *AJNR Am J Neuroradiol*. 2004;25(3):494-497.
9. Saito T, Nishioka M, Ogino M, Endo K, Kowa H. A case of hereditary motor and sensory neuropathy type I with optic atrophy, neural deafness and pyramidal tract signs. *Clin Neurol*. 1993;33(5):519-524.
10. Kulkarni SD, Sayed R, Garg M, Patil VA. Atypical presentation of Charcot-Marie-Tooth disease 1A: a case report. *Neuromusc Disord*. 2015;25(11):916-919.
11. Pareyson D, Taroni F, Botti S, et al. Cranial nerve involvement in CMT disease type 1 due to early growth response 2 gene mutation. *Neurology*. 2000;54(8):1696-1698.
12. Romano N, Federici M, Castaldi A. Imaging of cranial nerves: a pictorial overview. *Insights Imag*. 2019;10(1):33.
13. Martyn CN, Hughes RA. Epidemiology of peripheral neuropathy. *J Neurol Neurosurg Psychiatry*. 1997;62(4):310-318.

How to cite this article: Bartholomew RA, Zamani AA, Kim GS, et al. Prevalence and significance of cranial nerve imaging abnormalities in patients with hereditary neuropathies: Clinical implications at the skull base. *Laryngoscope Investigative Otolaryngology*. 2020;5:11–18. https://doi.org/10.1002/lio2.343