Cerebellopontine Angle Tumor in a Patient with a Maternally Inherited *SDHD* Gene Mutation

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Abstract: Acoustic neuromas are the most common tumor in the cerebellopontine angle (CPA) but are rare in the general population. Paragangliomas are rarer still and, in a minority of cases (20%), are known to be caused by errors in the *SDHD* gene. Mutations in this gene are highly penetrant when inherited paternally but not maternally. We present the first reported case of a patient with a CPA tumor and a maternally inherited *SDHD* gene mutation.

Key Words: acoustic neuroma; cerebellopontine angle (CPA) tumor; paraganglioma; *SDHD* gene; sensorineural hearing loss

Cerebellopontine angle (CPA) tumors are a relatively rare entity and typically are either idiopathic or due to spontaneous mutations in several genes. Ninety percent of CPA tumors are acoustic neuromas [1], which have an overall incidence of approximately 1 per 1 million in the population [2]. Meningiomas can also occur around the internal auditory meatus but are much less common, making up only 5% of internal auditory canal tumors. Ganglioneuromas have also been reported in the internal auditory canal but are exceedingly rare [3]. Even rarer are paragangliomas, known as *glomus tumor*s or *chemodectomas*, which have also been reported to occur in the CPA [4].

Genes that code for proteins in the mitochondrial electron transport chain complex II (e.g., *SDHB*, *SDHC*, and *SDHD*) are known to cause familial paraganglioma and pheochromocytoma. Mutations in *SDHB* and *SDHC* do not have parent-of-origin effect. *SDHD*, on the other hand, located on chromosome 11q23, is inherited in an autosomal dominant manner, with genomic imprinting playing a critical role in penetrance [5]. Literature suggests that, owing to a mutation in the *SDHD* gene, paragangliomas should occur only when inherited from the father [6]. No reported cases exist of a CPA tumor in a patient who inherited an *SDHD* mutation from his or her mother.

Only four cases of simultaneous acoustic neuroma and paraganglioma have been reported in the literature [7], and none was associated with *SDHD*. We present here the first reported case of a patient with a CPA tumor and a maternally inherited *SDHD* gene mutation.

CASE REPORT

The patient (RG) was a 44-year-old white man with a 4-month history of left-sided hearing loss and tinnitus. The patient had known congenital mental retardation due to hyaline membrane disease. Otological examination showed a normal tympanic membrane and middle-ear space. No other cranial nerve deficits were found on physical examination at presentation. Neck examination results were also negative for any masses. The audiogram showed a mild to moderately severe sensorineural hearing loss of the left ear, with normal hearing on the right. Audiometric brainstem response showed a delayed wave form in wave V of the left ear.

A computed tomography (CT) scan was performed with and without contrast rather than the preferred study

Figure 1. Contrasted computed tomography prior to gamma knife treatment. Cerebellopontine angle tumor can be visualized on the left.

Figure 2. Contrasted computed tomography 7 years after treatment. Comparison with Figure 1 indicates stable tumor.

of magnetic resonance imaging (MRI), because the patient had metallic fragments in his chest. The scan demonstrated a 1-cm enhancing left CPA tumor with an enlarged internal auditory canal that was consistent with an acoustic neuroma (Fig. 1).

The patient was observed for tumor changes, and a follow-up CT scan 7 months after the original study showed a growth rate of 1.14 mm annually. Surgical intervention and radiotherapy were then discussed with the patient and his family. Microsurgical resection was offered, but the patient requested the less invasive option of gamma knife stereotactic surgery instead.

Other than neuralgia in the distribution of cranial nerve VII, the patient has remained asymptomatic. Very little progression has been seen in hearing loss, with stable pure-tone averages, a 15- to 20-dB drop in hearing in the high frequencies and, actually, a temporary improvement in word recognition scores that appears to have been transient. Follow-up CT scans have demonstrated stability of the tumor (Fig. 2).

Seven years after successful gamma knife treatment of the CPA tumor, RG presented to our cancer genetics clinic secondary to a significant family history of paraganglioma. The patient's mother was treated for bilateral carotid body tumors (CBTs), and three of four of his living maternal aunts had either unilateral or bilateral CBTs. A maternal uncle tested negative for paraganglioma, and another maternal aunt died with no known disease prior to testing.

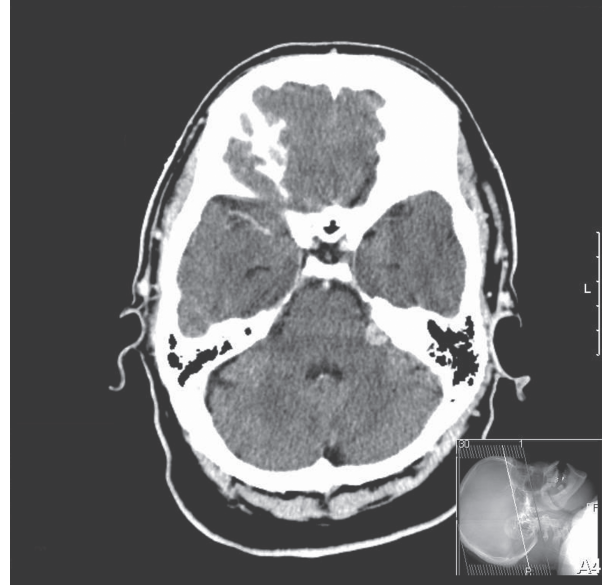Sequence analysis of the subject's *SDHD* gene identified a change of C to T at the second nucleotide of codon 81 in exon 3 in one copy of the gene (c.242C>T). This change results in a deletion, as it causes an amino acid change of proline to leucine (P81L). The same mutation was also present in RG's mother and all known affected family members.

DISCUSSION

RG presents as a unique case of an individual with a co-existing CPA tumor consistent with an acoustic neuroma and an *SDHD* gene mutation known to cause familial paragangliomas with paternal transmission. To date, constitutional mutations in *SDHD* have not been reported in any acoustic neuroma cases, and no reports exist of a CPA tumor in a patient who inherited a maternal mutation.

The specific genetic mutation found in RG's family, c.242C>T, has been identified in other patients reported by Baysal et al. in 2000 [8] and 2002 [9]; Badenhop et al. in 2001 [10]; and Milunsky et al. in 2001 [11]. The literature contains controversy regarding which genes on chromosome 11 are imprinted and how errors may occur somatically to cause the parent-of-origin effect [12–14]. Inherited paraganglioma tumor cells have a loss of heterozygosity of the normal maternal chromosome at 11q23 [8]; however, later studies indicate that the loss of heterozygosity at that locus is due to loss of the entire maternal chromosome 11 [14], not just the 11q23 region, which calls into question whether *SDHD* is actually maternally imprinted. *SDHD* appears to function as a tumor suppressor gene or in conjunction with a paternally imprinted tumor suppressor gene located on 11p15 [14]. With transmission of a paternal mutation

and loss of the wild-type maternal allele, an individual is predisposed to paraganglioma formation. Insufficient *SDHD* gene product along with loss of a maternally active tumor suppressor gene on 11p15 predisposes cells to sense a chronic hypoxia state, resulting in persistent stimulation and subsequent tumor formation. This is supported by the finding that higher altitudes are a contributing factor to phenotype severity in paragangliomas [15].

Hereditary paragangliomas are typically slow growing, benign, highly vascular tumors derived from neural crest cells and classified as neuroendocrine tumors. They are most commonly found in the head and neck but, because of their embryological origin, they may present anywhere from the internal auditory canal to the level of the kidneys. Most originate from the parasympathetic system and do not frequently secrete catecholamines. The carotid body is the most common site of origin in the head and neck. Approximately 10% of paragangliomas are malignant. Some 20–30% of cases are considered hereditary, though reports range from 10% to 50% [9].

Acoustic neuromas are the most common tumor in the internal auditory canal, estimated at approximately 90% of CPA tumors. The gold standard for diagnosis is an MRI with contrast; however, owing to MRI contraindications, a CT scan with contrast was used for diagnosis in the case of RG. The lesion was determined to be consistent with an acoustic neuroma, as reported by our neuroradiology team, but the possibility of a paraganglioma or other tumor type cannot be ruled out because tissue is not available for pathology. Such lesions as meningioma, ganglioneuroma, paraganglioma, lipoma, or metastatic tumor should present with a different history and imaging findings.

The treatment for acoustic neuromas can vary from observation to microscopic surgery or stereotactic radiation treatment (gamma knife). RG elected to pursue gamma knife treatment and has demonstrated no appreciable growth in tumor size for the last 7 years, on the basis of serial CT imaging. With this treatment modality, more than one-half of patients can expect to have a reduction in the size of the tumor, whereas approximately one-third will have no change in size, as is found with this case.

Benefits of early CPA or paraganglioma tumor detection include the possibility for early intervention—which may help to prevent hearing loss, vocal cord paralysis, facial nerve and hypoglossal dysfunction, and increased risk of bleeding—and the possibility of tumor resection. In male patients such as RG, who have an *SDHD* mutation inherited from their mother, routine screening for paraganglioma is thought to be unnecessary, as the literature has reported no case of such an individual's being affected by a paraganglioma. Our case calls this type of medical management into question.

RG's inherited *SDHD* mutation should be clinically silent owing to its maternal derivation, but the concomitant existence of a CPA tumor raises doubt. The possibility of a paraganglioma exists, but even if RG's tumor were confirmed to be an acoustic neuroma, the occurrence of the two events seen in our patient would be the first reported in the current literature. The possibility that the CPA tumor may not have been due to chance (somatic) occurrence and that *SDHD* could be involved in the pathogenesis of acoustic neuroma should be considered. Also, the possibility of two somatic events (i.e., loss of paternal 11q23 and maternal 11p15) in addition to the inherited maternal *SDHD* mutation could possibly cause a paraganglioma in the offspring.

In conclusion, physicians should be aware that familial paraganglioma is a recognized entity and should obtain a comprehensive family history from any patient presenting with a CPA tumor. An appropriate genetics referral and screening for pheochromocytoma or paraganglioma are strongly encouraged to improve patient care.

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