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ORIGINAL ARTICLE

The history of the glomus tumors – nonchromaffim chemodectoma: a glimpse of biomedical Camelot

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Abstract

Conclusions: Guild's initial 231 word report was the source of a stream of positive consequences; the glomus story is a paradigm of the utility of basic science. *Background:* The glomus tumor has had a number of different names, including glomus jugulare, glomus tympanicum, nonchromaffin paraganglioma, and carotid body tumor. Although they have occurred throughout the ages, glomus tumors were neither recognized nor understood until Harry Rosenwasser read Stacy Guild's report of 1941. *Materials and methods:* The pertinent literature from the 18th century to the present was reviewed. *Results:* Stacy Guild's pursuit of basic scientific knowledge laid the foundation for a chain of clinical and scientific advances that continue to the present and will continue to have positive effects into the future. Guild's brief basic science note of 1941 was used through the scholarship of Rosenwasser to define a clinical entity that had not been recognized. This new nosology, rapidly adopted worldwide, provided a biological basis for the rational grouping of patients and analysis of their ills. Subsequent to this, it was noted that many of these tumors occurred in families, apparently transmitted as an autosomal dominate but occurring primarily in the males. Further study based on these observations led to the identification of a genetic mechanism of inheritance: genomic imprinting. A further advance of the synergetic relationship between the environment – oxygen tension/altitude – and the mutation explains Guild's 1953 observations that all patients, without any sexual predominance, have glomus bodies but not all have tumors.

Keywords: *glomus tumor, Stacy Guild, genetic imprinting, Harry Rosenwasser*

Introduction

The glomus tumor has had a number of different names, including glomus jugulare, glomus tympanicum, nonchromaffin paraganglioma, and carotid body tumor. This paper will use the term glomus to include all of the nonchromaffin paraganglioma which arise in the ear. Although they have occurred throughout the ages, glomus tumors were not widely recognized nor understood until Harry Rosenwasser [1] read Stacy Guild's report of 1941 [2]. This initiated a series of discoveries which have led to identification of a previously unrecognized mechanism of genetic inheritance [3], and the discovery of the environmental and mutational synergy that accounts for the greater frequency of these tumors in males than in females, and also why the incidence of glomus tumors is increased among those living at higher altitudes [4].

Antiquity to 18th century

The first description of the carotid body, of which structure the glomus is a form of tumor, is attributed to the 1743 thesis of Taube [5]. There is in this thesis, however, no mention of pathology which can be considered to be that of the glomus jugulare or tympanicum.

19th century

The carotid body received a definitive description by von Luschka in 1862 and the first description of its tumor was that of Marchand in 1891 [6]. A review of Toynbee's [7] descriptive catalogue of 1659 temporal bones in 1857 reveals no identification of a pathology which may be consistent with a glomus tumor. Nor was any description of this tumor found in the late edition (1902) of Politzer's textbook [8].

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Grünwald mentions a polypoid-like angioma of the ear in 1891–1892 [9]; this is probably noted by Marx in 1926 who does not, however, give the Grünwald reference.

20th century

Beck [10], in a case report of 1906, mentioned that Weidner: '... has seen a true angioma, with new formations of blood vessels in middle ear tumors.'

Beck then described a 23-year-old woman with a left conductive hearing loss as evidenced by the Weber test in the left ear and a left-sided pulsitile tinnitus whose left external auditory canal was filled with a bluish-grey mass. He attempted to remove this mass, and described the initial procedure as follows:

> 'Operation: A blunt-pointed probe found the growth to be firmly attached anteriorly and about one inch from the external meatus. Bleeding following this procedure was considerable. I applied rapidly a Blake's polyp snare, and removed a part of the tumor the size of a pea. This was followed by a hemorrhage, such as one finds in opening the jugular or lateral sinus.... Consequently, I packed the ear firmly with the aid of external compression; put patient to bed.'

According to the pathology report, it was: '... a very vascular tumor with many small cells ...'

The symptoms, signs, physical examination, operative findings, and the pathology note are all consistent with the findings of a middle ear glomus. He followed the patient for more than a month and the only complication was a left facial paralysis. The patient's hearing improved and there was no mention of the pulsitile tinnitus.

Lubbers [11] in 1936 presented a case report at the 62nd annual meeting of the Dutch Otolaryngological Society in Utrecht which described a glomus tumor in a woman who died 4 days postoperatively from brain infarct as a consequence of the ligation of the right common carotid artery. The publication was in Dutch and is not found in major reference databases. It was cited, with histopathology, by Gerlings in 1979 [12].

Recognition

A 231 word note, in 1941, published by Stacy Guild PhD (Figure 1A) in the *Anatomical Record* is the first recognition of structure which resembles the carotid body in the ear [2].

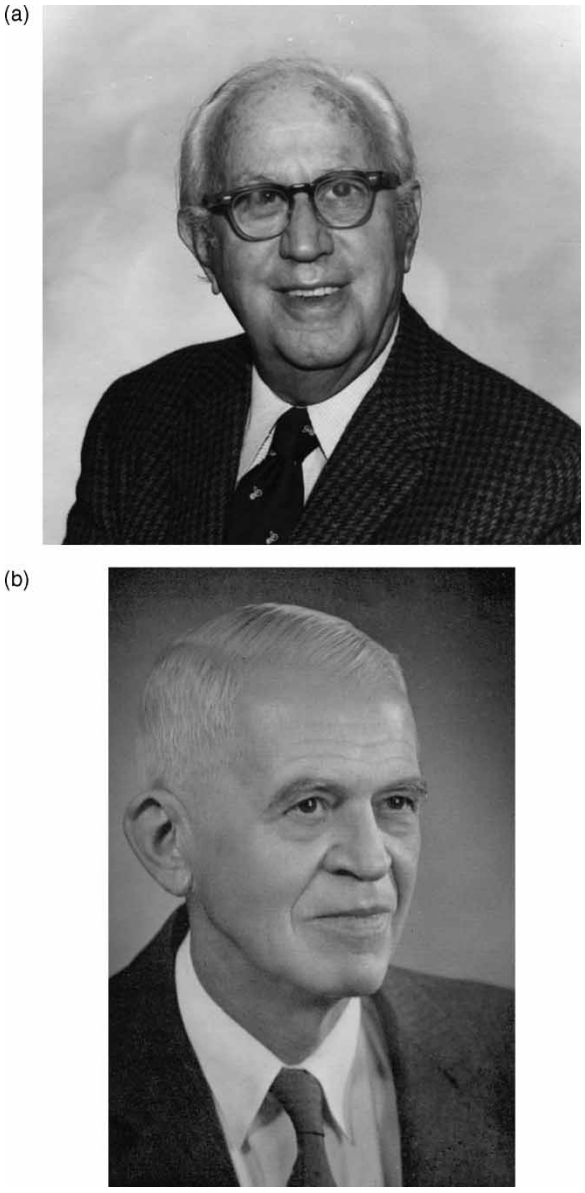

Figure 1. (A) Stacy Rufus Guild, PhD (1890–1966) (from Bordley JE. Stacy Rufus Guild, Ph.D., 1890–1966. Ann Otol Rhinol Laryngol 1966;75:1176–80). (B) Harry Rosenwasser, MD (1902–1987) (from the John Q. Adams Center for the History of Otolaryngology–American Academy of Otolaryngology and Head and Neck Surgery).

> 'Human temporal bone sections reveal structures, in several respects like the carotid body, for which the name glomus jugularie is proposed. Usually they are in the adventitia of the dome of the jugular bulb, immediately below the bony floor of the middle ear and near the ramus tympanicus of the glossopharyngeal nerve. Usually there is but a single flattened ovoid glomus, about 0.5 mm. in the longer diameters and about 0.25 mm. thick. Occasionally two or more smaller bodies are present, sometimes one or all are in the canal

that transmits the ramus tympanicus through the floor of the middle ear (in one case also along the course of this nerve over the cochlear promontory).

Each glomus, wherever located, consists of blood vessels of capillary or precapillary caliber with numerous epithelioid cells between the vessels. Usually, but not always, the vessels are the more prominent feature. Innervation and blood come from the same trunks that supply the carotid body; namely, glossopharyngeal nerve and ascending pharyngeal artery (through its inferior tympanic branch).

This structure has as yet been studied only in 24 μ sections of decalcified material stained with Ehrlich's hematoxylin and eosin, and has not been sought for in forms other than man. Presumably it has functions like the carotid body, perhaps limited to a smaller circulatory region. Suggestion: similar structures may be present along other parts of the peripheral circulatory system.'

Four years latter, in 1945, Rosenwasser (Figure 1B) published the first case report of a middle ear tumor in a 36-year-old man now clearly recognized as a glomus tumor [1]. The patient presented with a left facial paralysis, a mass in the left external auditory canal and a left-sided hearing loss. There was no mention of tinnitus. The patient was operated on April 18, 1942. A large purple mass was found in the middle ear attached to the hypotympanum. The floor of the middle ear was dehiscent and only that portion of the tumor which was in the middle ear was removed. The story of the diagnosis and care of the case, with a 30-year follow-up, has been preserved through the Oral History Program of the Foundation of the American Academy of Otolaryngology–Head and Neck Surgery (AAOHNS) [13]. A pertinent portion of the transcript from the interview conducted by Avrim R. Eden on September 10, 1985, is as follows:

'EDEN: Dr Rosenwasser, tell us a little about glomus jugulare tumors, and your first patient that you saw, and how everything went from there.

ROSENWASSER: This is, I think, an interesting story and has many, many facets which I've enjoyed thinking about over the years. But in 1941 a patient came to the hospital because he had been examined by his draft board, and they rejected him because he had polyp, they said, in his ear canal. He then went to a doctor who put a snare around – or took a piece of it – and this was followed by horrendous bleeding, and he came here.

When I saw him here, I thought he had a chronic ear with polyps and infection, etc. We admitted him to the service. When we worked him up, we found he had a huge defect. I operated on him, and when I got in there, this defect, which was as big as a large cherry, was attached to the carotid artery and jugular bulb. So I put an artery clamp over it, and took the top off because I couldn't do anything until I got some room and controlled the bleeding. And clinically, I thought this is a malignant tumor with a bone defect and polyps and granulations. Probably a hemangioma.

We cleaned out the rest of the mastoid cavity and sent the specimen over to Dr [Sanado] Otani]. And Otani called me in great excitement. He said, "Where did this come from?" And I said, "It came from the mastoid, attached to the jugular bulb, and the facial [nerve] was involved." He said, "The mastoid?" "Yes, the mastoid." Anyhow, we had great discussions about this and finally I said, "Well, this is a hemangioma, and I want him to get x-ray [treatments] because we're going to be in trouble." So I talked Bill Harris into radiating him. And finally, Otani said, "This is a carotid-body-like tumor." How does it get to the middle ear? We didn't know, so we did nothing about it.

Four years later, we came across an article in the Anatomical Record written by Stacey Guild of [The] Johns Hopkins [University], in which he described a structure similar to the carotid body, localized in the floor of the middle ear, adjacent to the jugular bulb. He didn't find it in all the specimens; it was present in some. Now, that's when Otani and I got together, and I said, "Dr Otani, he could have developed this tumor from this kind of structure." And he agreed. And I said, "Let's report it." He said, "No, you report it. This is a clinical case. You report it." The reason I say so many things about this. . . . Now, today it is so unlike people to be like Otani was. This was something – he wasn't worried that it was a first case or second case or anything. And that's why when I wrote my monograph on glomus tumors, there's a picture of Otani there telling this whole story. That's the background.'

Guild [14], in1953, stated that there was correspondence concerning Rosenwasser's case (Figure 2): 'After correspondence with me, he (Rosenwasser) suggested in his report of the case that the tumor may have arisen from a glomus

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Baltimore-5, Maryland

April 27, 1945.

Dear Dr. Rosenwasser:

Thanks for the two reprints. The one on carotid body tumor naturally is of the most interest to me; I had read it carefully when the journal appeared, and intended to write you then, but just didn't get around to do so. What I wanted to tell you was that I agree with you that the structure I reported as normal for the region may well be at the basis of the tumor in your patient. I am sorry that the rush of more urgent work has prevented, thus far, charging the study further than the preliminary report. I have seen the structure in many more cases since then, and have tried some silver staining on it, but nothing worth a further report.

If you are ever down here, I'll be glad to show you some of the sections, so you can make a direct comparison of his older structure with the tumor. By the way, if you do come, please bring along a section of the tumor, so that I also can make a direct comparison.

Sincerely yours,

Stacy V. Guild

Figure 2. Personal letter from Stacy Guild to Harry Rosenwasser telling of Guild's interest in his reported case (from H. Rosenwasser, Glomus jugulare tumors. I. Historical background, Arch Otolaryngol 1968;88(no. 1).

jugularis instead of from the carotid body which it resembled histologically.'

Guild's article went on to describe the findings in a series of 88 ears which had been serially sectioned and stained with Ehrlich's hematoxylin and eosin. In all, 248 glomus formations were found along the nerve of Jacobson-tympanic branch of the glossopharyngeal nerve and nerve of Arnold-auricular branch of the vagus nerve. It was observed that glomus bodies on the nerve of Arnold are probably innervated by the glossopharyngeal nerve. There were on the average 2.82 glomus bodies per ear, with no difference between the sexes. There may have been some small increase in the number of glomus formations in the middle age group, 30–39 years. The glomus body was absent in $<5\%$ of ears; this may be artifactual as the sections were cut at 24 μ and only every 10 sections were examined.

Dissemination and care

Soon thereafter there were numerous reports of the glomus tumor by Rosenwasser [15] and others, e.g. Graf [16]. Rosenwasser maintained his interest in the tumor with documentation of metastasis in 1958, and long-term follow-up in 1969 [17].

The history of the management of glomus tumor of the ear was presented by Michael and Robertson in their article of 2004 [18], which includes a description of the development of current care modalities. A major adjuvant to care is the use of preoperative super-selective embolization, first used in 1973 for these tumors by Hekster et al., and now routine. Radiation therapy was used by Rosenwasser in his original case and has been used since as an alternative to surgical excision. A major challenge in evaluating the efficacy of interventions of these tumors is that they can recur [19]. The development of surgical approaches was stimulated by the development of skull base surgery in the latter part of the 20th century, and greatly enabled by improved imaging techniques. The present technique for the more complex tumors was described in 2002 by Al-Mefty and Texeira [20]. The gamma knife has been used, and has been shown to retard tumor growth.

Genetic understanding

Carotid body tumors have been recognized as occurring in families since the 1930s [21]. A report by Goekoop in 1932 of three sisters with ear tumors may, in retrospect, represent glomus tumors [22]. Although the occurrence in sisters living at a low altitude is somewhat anomalous, Goekoop's description of the evolution of the tumor, its presentation in the external and middle ear, and slow growth all are consistent with glomus.

The first documented report of autosomal dominant transmission of glomus was in 1980 [23] and in 1981 by second unrelated kindred.

As can bee seen in Figure 3, there many more affected males than females. Van Baars et al. reported a male/female ration of 20:6. This observation led to an extensive study of Dutch cohorts at the University of Leiden. Van der Mey et al. [3] in 1989 used these data to describe a new mechanism of inheritance, genomic imprinting, as follows:

> 'A study based on fifteen pedigrees showed that familial glomus tumors are inherited almost exclusively via the paternal line, a finding inconsistent with autosomal dominant transmission. The results can be explained in terms of the genomic imprinting hypothesis – the maternally derived gene is inactivated during female oogenesis and can be reactivated only during spermatogenesis . . .'

The hereditary glomus tumors (paragangliomas, PGL, MIM no.168000) were mapped to 11q23 [24].

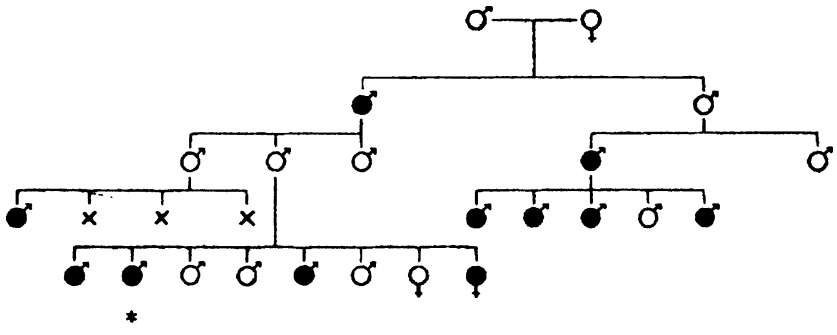

Figure 3. Family tree of the first reported genetic occurrence of the glomus tumor – non chromophin chemodectoma. X, no information; *, index case with glomus; ●, bilateral carotid body tumors. (From D.T. Pereira and R.D. Hunter, Familial multicentric non-chromaffin paragangliomas: a case report on a patient with glomus jugulare and bilateral carotid body tumors, Clin Oncol 1980;6(no. 3).

21st century

Molecular genetics of the glomus tumors were reported by Baysal et al. in 2000 and 2002 [25]. There are two mutated genes, the SDHD and the SDHB; these mutations appear only in the cases with familiar occurrence. Environmental factors appear to contribute to the expression of the non-sense and splicing mutations. It has been postulated that the higher the altitude (i.e. the less the oxygen) the greater the severity of the glomus gene (PGL1(4)).

Conclusion

Stacy Guild's pursuit of basic scientific knowledge laid the foundation for a chain of clinical and scientific advances that continue to the present and will continue to have positive effects into the future. Guild's brief basic science note of 1941 was used through the scholarship of Rosenwasser to define a clinical entity that had not been recognized. The new nosology, rapidly adopted worldwide, provided a biological basis for the rational grouping of patients and analysis of their ills. Subsequent to this, it was noted that many of these tumors occurred in families, apparently transmitted as an autosomal dominate but occurring primarily in the males. Further study based on these observations led to the identification of a genetic mechanism of inheritance, i.e. genomic imprinting. A further advance of the synergetic relationship between the environment – oxygen tension/altitude – and the mutation explains Guild's 1953 observations that all patients, without any sexual predominance, have glomus bodies but not all have tumors. Guild's initial 231 word report was the source of a stream of positive consequences; the glomus story is a paradigm of the utility of basic science.

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