ORIGINAL ARTICLE

What Is the Real Incidence of Vestibular Schwannoma?

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Objectives: To present the incidence of vestibular schwannoma (VS) in Denmark, compare the incidence with that of previous periods, and discuss the real incidence of VS.

Design, Setting, and Patients: Prospective registration of all diagnosed VS in Denmark, with a population of 5.1 to 5.2 million, during the 6 years from January 1996 through December 2001. Incidence in this period was compared with that of 3 previous periods (July 1976 through June 1983 [first period], July 1983 through June 1990 [second period], and July 1990 through December 1995 [third period]).

Results: In the 1996-2001 period, 542 cases of VS were diagnosed, representing a mean incidence of 17.4 VS/1 million inhabitants per year. Of these, 227 tumors underwent operation, 14 underwent irradiation, and 301 were allocated to observation (wait-and-scan policy). One hundred sixty-six tumors were intrameatal. Size of extrameatal tumors was small in 104; medium in 194; large in 68; and giant (>40 mm) in 10. Compared with incidences of 7.8 VS/1 million inhabitants per year in the first, 9.4 VS/1 million inhabitants in the second, and 12.4 VS/1 million inhabitants in the third periods, the incidence for the 1996-2001 period represents an increase to 17.4 VS/1 million inhabitants per year. The mean incidence for the entire 25.5-year period was 11.5 VS/1 million inhabitants per year.

Conclusions: An estimate of a realistic mean incidence of VS depends on the observation period. Our 25.5-year registration of an entire population showed a mean incidence of 11.5 VS/1 million inhabitants per year. However, the latest period registered represents an incidence of 17.4 VS/1 million inhabitants per year, which, combined with a probable further increase of diagnosed tumors in forthcoming years, suggests a realistic incidence of approximately 13 VS/1 million inhabitants per year.

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In Denmark, with a population ranging from 5.1 million to 5.2 million, a uniform public health care system, and the introduction of translabyrinthine surgery in 1976, we have been able to register prospectively all diagnosed vestibular schwannomas (VS) in the entire country. During the first 7-year period from July 1976 to June 1983, the incidence was 7.8 tumors/1 million inhabitants per year.[1] During the second 7-year period from July 1983 to June 1990, it increased to 9.4 tumors/1 million inhabitants per year,[2] and during the third 5.5-year period from July 1990 to December 1995, the incidence increased even further to 12.4 tumors/1 million inhabitants per year.[3]

The goal of this report is to describe and analyze the further increase of the incidence of VS during the fourth 6-year period from January 1996 to December 2001. Such analysis is not only of academic interest, but may be very important in discussion of tumor growth and indication for surgery or radiotherapy for VS. Furthermore, we will discuss the accuracy of various mean incidences in various observation periods and indicate a range of the true incidence.

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Some previous studies on incidence of VS are based on epidemiological studies of brain tumors. Kurland[4] found 27 primary brain tumors among 30 000 inhabitants in Rochester, Minn, during a 10-year period, 2 of which were VS. Based on these 2 VS, the annual incidence per 1 million inhabitants would amount to 7 VS. In Connecticut, Schoenberg et al[5] found an incidence of 1VS/1 million inhabitants per year from 1935 to 1964. In Israel, Cohen and Modan[6] found an incidence of 4 VS/1 million inhabitants per year from 1960 to

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1964. In Wessex, England, Barker et al[7] found 4 VS /1 million inhabitants per year from 1965 to 1974. In Manitoba, Canada, 5 VS/1 million inhabitants per year were found from 1980 to 1985,[8] and 13 VS/1 million inhabitants per year were found from 1987 to 1995.[9] This incidence was based on registration of 71 VS at a neurosurgical department in a community of 1 million inhabitants.

Some other studies, like ours,[1-3] are based on registration of diagnosed VS only. Nestor et al[10] found an incidence of 12 VS/1 million inhabitants per year from 1985 to 1988 in a North American community with 2 million inhabitants; this incidence was based on 69 VS. In the County of Aarhus, Denmark, with a population of 600 000 inhabitants, an incidence of 18 VS/1 million inhabitants per year was found, based on 53 diagnosed VS from 1992 to 1995.[11] In that region, the incidence of VS in the 1970s was 5 VS/1 million inhabitants per year, and in the 1980s it was 7 VS/1 million inhabitants per year,[1,2] indicating that this strong increase of incidence is coming from a pool of previously undiagnosed VS. Moffat et al[12] found 230 VS from 1981 to 1991 and an incidence of 20 VS/1 million inhabitants per year in the Cambridge region of England, which has a population of 2 million inhabitants. The authors reported that their findings were the result of a precise diagnostic strategy in which magnetic resonance imaging (MRI) was the first investigation used for asymmetric hearing loss.

Howitz et al[13] analyzed 795 VS registered in Denmark from 1977 to 1995 by the Danish Cancer Registry, supplemented and completed by the clinical database established at our department.[1-3] The incidence was 5 VS/1 million inhabitants per year from 1977 to 1981, 8 VS/1 million inhabitants per year from 1982 to 1986, and 10 VS/1 million inhabitants per year for 1987 to 1991 and 1992 to 1995.

Recently, the epidemiology of VS in Poland (population, 38.5 million) was evaluated by a questionnaire on the number of VS undergoing operation during a 12-month period from 1997 to 1998, which was answered by 7 neurosurgical departments and 3 ear, nose, and throat centers. In total, 72 tumors underwent operation, amounting to a surgical incidence of 1.9 VS/1 million inhabitants per year.[14]

The various mean incidences, ranging from 2 to 20 VS/1 million inhabitants per year, from various periods and places, indicate that the real incidence of VS is unknown, and that huge differences in reported incidences exist today.

METHODS

As in the 3 previous periods,[1-3] all 542 patients with newly diagnosed VS in the 6 years from January 1996 to December 2001 were prospectively registered. Most intrameatal and small tumors did not undergo operation, but were allocated to observation (wait-and-scan management) (**Table 1**). Most giant and large tumors underwent operation by means of the translabyrinthine approach, and a few by means of the suboccipital or middle fossa approach. Radiotherapy was performed in a few cases. After information about the disease was provided to the patient and the advantages and disadvantages of various treatment modalities were discussed, we followed up and respected the patients' choice of treatment.

Table 1. Management of VS Diagnosed in Denmark Between January 1996 and December 2001*

		Extrameatal Extension (mm)				
Management	Intrameatal	Small (1-10)	Medium (11-25)	Large (26-40)	Giant (>40)	Total
Operation						
Translabyrinthine	11	27	102	59	9	**208**
Suboccipital	1	0	3	2	1	**7**
Middle fossa	4	7	1	0	0	**12**
Radiotherapy	2	1	11	0	0	**14**
Wait and scan	148	69	77	7	0	**301**
Total	**166**	**104**	**194**	**68**	**10**	**542**

Abbreviation: VS, vestibular schwannoma.
*Data are expressed as number of tumors.

All demographic data about the patient, symptoms, and tumor size were registered and stored in a database.

RESULTS

Compared with the previous 3 periods,[1-3] the total number of diagnosed VS had increased to 542 tumors in the fourth period (**Table 2**). The mean incidence in the fourth period increased to 17.4 VS/1 million inhabitants per year (**Figure 1**), and the mean number of diagnosed tumors per year increased to 91.

The size of the diagnosed tumors has gradually decreased through the 4 periods (Table 2). In the first period, the giant and large tumors dominated; in the second period, a significant decrease of the giant tumors and an increase of the small tumors occurred ($P<.001$, χ^2 test). In the third period, there was a significant decrease of giant tumors and increase of intrameatal and small tumors ($P<.001$). In the fourth period, there was a highly significant increase of intrameatal tumors and decrease of giant tumors ($P<.001$). The 166 intrameatal tumors represent nearly one third of all tumors (Table 2), which is an enormous increase, compared with 0.4% in the first and 0.3% in the second periods.

The percentage of giant tumors decreased to 1.8%, a considerable and significant decrease ($P<.001$) in relation to the first period with 36.3% giant tumors (Table 2).

Mean size of the extrameatal tumors at diagnosis has gradually decreased for each period, from 28 mm in the first period to 16 mm in the fourth period (**Figure 2**).

COMMENT

To illustrate the constantly increasing incidence, the VS can be classified into several categories from the epidemiological point of view. The first category is asymptomatic or silent VS, without any subjective or objective symptoms. We do not know the prevalence or incidence of these VS, or the duration of the asymptomatic period. In addition, we do not know whether all asymptomatic VS will become symptomatic with time. We can imagine, however, that all symptomatic VS have had an initial silent or asymptomatic period and that asymptomatic VS represent a pool of tumors that may become symptomatic. Whether this happens depends on the pa-

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Table 2. Distribution of VS of Various Sizes in Each of the 4 Periods*

Period (No. of VS)	Intrameatal	Extrameatal Extension (mm)				Total†
		Small (1-10)	Medium (11-25)	Large (26-40)	Giant (>40)	
July 1976 through June 1983 (n = 278)	0.4	13.3	25.5	24.5	36.3	**100.0**
July 1983 through June 1990 (n = 337)	0.3	21.1	28.8	28.2	21.7	**100.0**
July 1990 through December 1995 (n = 355)	7.9	29.0	31.5	19.2	12.4	**100.0**
January 1996 through December 2001 (n = 542)	30.6	19.2	35.8	12.6	1.8	**100.0**
All 4 periods (n = 1512)	13.0	20.8	31.4	19.8	15.1	**100.0**

Abbreviation: VS, vestibular schwannoma.
*Data are expressed as percentage of tumors.
†Because of rounding, percentages may not all total 100.

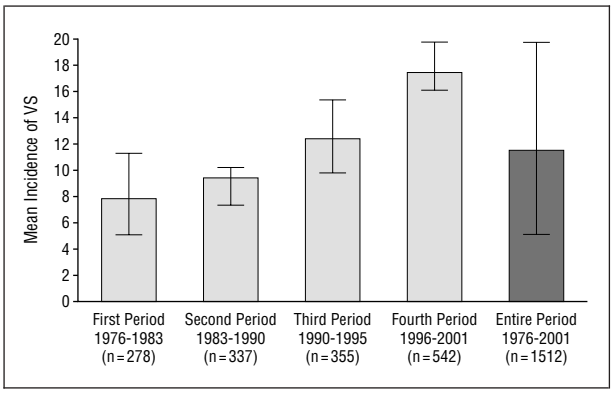

Figure 1. Mean incidence of vestibular schwannoma (VS) during various periods (newly diagnosed tumors per 1 million inhabitants per year). The parenthetical number below each bar indicates the total number of tumors diagnosed in the corresponding period. Error bars indicate range.

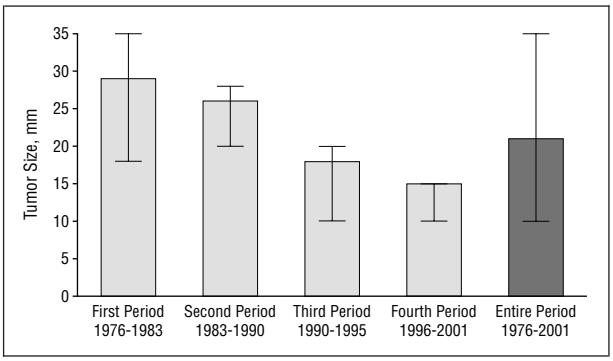

Figure 2. Median size of the extrameatal tumors during the various study periods. Error bars indicate range.

tient's own recognition of the symptoms, which can vary enormously, depending on culture, education, socioeconomic conditions, availability of health care services, and many other factors. Some asymptomatic VS may be discovered incidentally.[15]

Symptomatic, undiagnosed VS with an unknown prevalence and incidence represent another pool of VS, attributed to the patient's or the physician's delay, or both. This pool in Denmark is supposed to have become gradually smaller during the past 25 years, simply because the incidence of diagnosed tumors has increased (Table 2 and Figure 1). This occurred initially because of easier access to computed tomographic scanning and improved quality of the following generations of computed tomographic scanners, and later in the 1980s and 1990s because of the availability of MRI scanning and, later, MRI scanning with gadolinium enhancement. Other important factors are greater awareness on behalf of the patients and the physicians and the formation of various associations of patients with symptoms of hearing loss and balance disorders, such as the Acoustic Neuroma Association, Meniere Association, and Tinnitus Association. In particular, the Tinnitus Association may have influenced many patients with slight tinnitus to undergo MRI scanning, partly explaining the many intrameatal VS diagnosed in the last period (Table 2). Thus, such initiatives may have accelerated diagnosis of VS from the pool of nearly asymptomatic VS.

Diagnosed VS has a continuously increasing incidence in each period of up to 17.4 VS/1 million inhabitants per year in the last period (Figure 1). The mean incidence in the entire 25.5 years from July 1976 to December 2001 is 11.5 VS/1 million inhabitants per year, which is an increase compared with the previously published mean incidence of 9.8 VS/1 million inhabitants per year,[3] based on the 19.5 years of the first 3 periods from July 1976 to December 1995. The high increase of the incidence in the fourth period to 17.4 VS/1 million inhabitants per year has considerably elevated the mean incidence for the entire 25.5-year period.

We have several indications that the continuous increase of incidence is still due to the diagnosis of previously undiagnosed tumors. Among the first 69 translabyrinthine cases from the first period, the patient's mean delay in diagnosis was 7 years and the physician's mean delay was 6 years, for a total mean of 13 years. In the 300 cases that followed, 22% were diagnosed within the first symptomatic year. In the remaining 78% of patients, there was a mean total delay of 7.1 years,[16] including the patient's delay, the physician's delay, or both. The diagnostic delay became shorter with time, and among 703 patients with VS operated on by translabyrinthine approach, the diagnostic delay was shorter than 1 year in 25%, 1 to 5 years in 43%, and longer than 5 years in 32%. However, no statistically significant differences (χ^2 test, $P>.05$) in the length of patient history were found when the patients were grouped consecutively.[17] In the most recent period, in which the overall incidence and number of intrameatal tumors has further increased and the extramea-

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Table 3. Vestibular Schwannoma (VS) in Denmark, 1957-2001*

Period	No. of Years	No. of VS		VS by Projected Mean Incidences†		
		Diagnosed	Incidence†	13	16	20
January 1957 through July 1976[3]	19.5	585/30	5.4	1306/67	1599/82	2001/103
June 1976 through December 2001	25.5	1512/59	11.5	1709/67	2091/82	2626/103
Total	**45.0**	**2097/47**	9.1	**3015/67**	**3690/82**	**4627/103**

*Unless otherwise indicated, data are expressed as total number/mean number of VS per year.
†Calculated as number of VS per 1 million inhabitants per year.

tal size has further decreased (Figures 1 and 2 and Table 2), the diagnostic delay has continued to decrease. Several other authors have previously documented this process of quicker diagnosis. As an example, 1070 patients with unilateral sensorineural hearing loss undergoing screening by means of high-resolution fast-spin echo MRI were found to have a 5.2% incidence of VS.[18]

THE UNREALISTIC INCIDENCE IN TEMPORAL BONE STUDIES

As reviewed earlier,[3] the incidence of VS in temporal bone studies is extremely high, ranging from 0.8% to 2.7%, simply because these studies were based on selected temporal bones, collected through many years. Thus, the Wittmaack collection, with an incidence of VS of 1.7%, was based on 1720 temporal bones collected in Hamburg, Germany, from 1906 to 1945. The 2 collections at The Johns Hopkins University Hospital, Baltimore, Md, with incidences of 2.7% and 0.8%, represent 250 and 240 temporal bones, respectively, collected from 1928 to 1941. The collection of the Harvard Medical School, Boston, Mass, contains an incidence of 0.9%, and the Copenhagen, Denmark, collection contains an incidence of 2.4%, based on 150 temporal bones. After converting these data into incidences, the collection with the relatively lowest number of VS represents an incidence of 8000 tumors/1 million inhabitants per year, which is completely unrealistic. In the only existing study,[19] constituting 315 temporal bones from 176 consecutive autopsies, no tumors were found. Because the real incidence presumably lies around 13 VS/1 million inhabitants per year, several thousand consecutive autopsies of a randomized population are needed to eventually find the incidence of asymptomatic tumors.

WHAT HAPPENED WITH THE UNDIAGNOSED TUMORS?

The increasingly high mean incidence reveals the problem concerning tumor growth, ie, what happens with the undiagnosed tumors. Did the patients from the oldest period die with the tumor or because of the tumor? We believe that the former is the case. Because we have been involved in the diagnosis and management of VS for 40 years, we would have noticed if a high number of patients died of a VS at the hospitals, especially as vivisection with opening of the cranium was a routine procedure during the first periods. Therefore, we believe that most of the patients with undiagnosed VS died with the tumor. However, no systematic studies of vivisection records have been performed in our country or reported in the literature.

One intrameatal tumor each was diagnosed during the first and second observation periods, whereas 166 intrameatal tumors were diagnosed in the fourth observation period (Table 2). This indicates that most intrameatal tumors have grown extremely slowly.

IS THE TRUE INCIDENCE THE MOST RECENT ANNUAL INCIDENCE?

One may argue that the most accurate incidence derives from the most recent annual incidence, with the most advanced technologies available and easy access to health care, eg, 20 VS/1 million inhabitants per year, as we found in the last year of this survey (2001). This will be the simplest assumption, but then we have to explain what happened to a couple thousand undiagnosed tumors from the previous periods[3] (2530 VS; **Table 3**). If these tumors are assumed to be growing, they would be diagnosed today as large or giant tumors, and this is not the case (Table 2). If these tumors are not growing, they would all exist today as small tumors without significant symptoms that would lead the patient to a physician, or the patients would have died with or of the tumor. We find this highly unlikely, as argued already.

In our calculation, the highest realistic mean incidence could be 15.3 VS/1 million inhabitants per year. If the assumed incidence is greater than 16%, the number of previously undiagnosed tumors would increase accordingly, stressing the earlier comment even further. Where have these thousands of tumors gone? Have all these patients died with or of the tumor, unacknowledged by our health care system and especially our vivisectioning pathologists? We believe this is impossible.

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