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Authors

Peris-Celda, Maria
Graffeo, Christopher S
Perry, Avital
et al.

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Main Symptom that Led to Medical Evaluation and Diagnosis of Vestibular Schwannoma and Patient-Reported Tumor Size: Cross-sectional Study in 1,304 Patients

Maria Peris-Celda[1] Christopher S. Graffeo[1] Avital Perry[1] Panagiotis Kerezoudis[1] Nicole M. Tombers[2] Matthew L. Carlson[2] Michael J. Link[1]

[1] Department of Neurologic Surgery, Mayo Clinic, Rochester, Minnesota, United States
[2] Department of Otolaryngology–Head and Neck Surgery, Mayo Clinic, Rochester, Minnesota, United States

Address for correspondence Michael J. Link, MD, Department of Neurologic Surgery, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, United States (e-mail: link.michael@mayo.edu).

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Abstract

Objectives Although vestibular schwannomas (VS) are known to cause cranial nerve deficits, cerebellar symptoms, and hydrocephalus, the role of these symptoms as the key driver of presentation from the patient's perspective has not been described. Our objective was to survey a large, retrospective VS cohort to document the patient-reported principal initial symptom, and self-reported tumor size, and to study trends in VS patient presentation.

Methods Patients diagnosed with VS at our tertiary referral center and belonging to the Acoustic Neuroma Association (ANA) answered a questionnaire between 2015 and 2017. Demographic data, self-reported tumor size, and symptomatology were analyzed.

Results 1,304 patients completed the questionnaire. Tumors were diagnosed from 1966 to 2017 at a mean 51.8 years (range: 8–86 years); 66% were female, and 1.1% had confirmed neurofibromatosis type 2 (NF2). Tumor size was reported using a 6-point scale: 0 to 1 cm (22.9%), 1 to 2 cm (28.7%), 2 to 3 cm (20.5%), 3 to 4 cm (10%), greater than 4 cm (7.2%), and unknown (10.6%). Hearing loss was the most common symptom that led to diagnosis (51.5%), followed by dizziness (17%), tinnitus (11.2%), and incidental diagnosis (10.2%); a fraction that has increased significantly in the last decade ($p = 0.022$). Larger tumors and NF2 were significantly associated with young age ($p < 0.001$).

Conclusion Our large-scale questionnaire-driven review of 1,304 patients confirms that VS presentations are stereotypical, with most individuals recalling hearing loss, dizziness, or tinnitus as their chief complaint. Many tumors were incidentally diagnosed; an expanding population, attributable to increased access to magnetic resonance imaging (MRI). Large tumors were significantly more prevalent among younger patients at diagnosis, excluding NF2 patients, suggesting a more aggressive tumor biology that remains incompletely understood.

Keywords
- vestibular schwannoma
- hearing loss
- dizziness
- symptoms at presentation
- acoustic neuroma

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Introduction

The most commonly reported symptoms associated with vestibular schwannomas (VS) at the time of presentation are cranial nerve deficits, cerebellar symptoms, and hydrocephalic features, in addition to a small but significant fraction of patients whose tumors are incidentally identified.[1,2] Although hearing loss is the most frequently captured symptom at diagnosis, multiple comorbid symptoms are commonplace, yet the chief complaint driving the patient to seek medical attention and ultimately leading to the diagnosis has not been studied.[1–3] This subtlety is critical to better assess, as it may identify opportunities for earlier diagnosis and intervention, particularly given that delays in presentation by the patient or appropriate imaging by the primary physician are likely attributable to minimize certain symptoms, or the broad spectrum of neurologic conditions that share these clinical manifestations.

Although medical records frequently capture the breadth of presenting symptoms, the nuance of which disease feature had been primarily responsible for presentation and diagnosis is not always clear, and therefore previously unreported. By contrast, retrospectively collected survey data provides an opportunity to directly address questions that are so specifically focused on the patient experience, a research methodology that is powerfully enhanced in the assessment of low-incidence diseases like VS via patient run associations or support groups that empower the collection of data from large populations in a manner not restricted to an institution, or a single surgeon's experience.[4–7]

With these principles in mind, our objective was to retrospectively review a large cohort of VS patients, and capture the most common chief complaints underlying their presentation. In other words, the driving symptom that eventually leads to the VS diagnosis as well as the self-reported tumor size at diagnosis, to better understand trends in disease presentation and natural history, identify possible opportunities for earlier intervention, and correlate patient presentation characteristics with age and year of diagnosis.

Methods

Patients diagnosed with VS at our tertiary referral center and/or belonging to the Acoustic Neuroma Association (ANA) answered the "Mayo Clinic Acoustic Neuroma Quality of Life Survey," a multiple-choice questionnaire, circulated from 2015 to 2017. The ANA is a North American based, nonprofit organization with more than 5,000 members with the main objective to provide information about VS and its treatment.[8] The questionnaire was sent to 6,785 patients belonging to the ANA by email. Patient identifiers were crosschecked to ensure accurate deduplication (e.g., patients could only report their data one time). The questionnaire consists of 64 questions divided into four sections; for the present analysis, we abstracted and analyzed demographic data, self-reported data related to the tumor, date of diagnosis, and symptomatology (►**Table 1**). Descriptive and statistical analysis was performed with SPSS version 22 (Armonk, NY, IBM Corp.; ►**Table 2**). Chi-square test was used for categorical variables, and *t*-test and ANOVA (analysis of variance) were used for continuous variables (►**Table 3**). The results were considered significant when *p*-values were < 0.05. All pertinent study components were fully approved by our institutional review board (IRB 14–009331)

Results

Demographics

One thousand three hundred and four patients completed the initial questionnaire during the study period, from 2015 to 2017. The overall cohort included 432 (33.1%) treated at our institution, and 872 (66.9%) ANA members diagnosed and treated at other institutions in the United States and Canada. The response rate for the patients belonging to the ANA was 12.8%. The response rate from the patients treated at our institution was not recorded. VS were diagnosed during 1966 to 2017, at a mean age of 51.8 years (range: 8–86 years). Eight hundred and sixty-one (66%) were female. The time from diagnosis to survey was 5.5 years $\pm$ 7.4 (range: 0–49 years; ►**Table 2**).

Self-Reported Tumor Laterality and Size

Six hundred and thirty-five patients (48.7%) reported right sided tumors, 652 (50%) reported left sided tumors, and 14 (1.1%) had bilateral disease (three unanswered). Twenty-three patients (1.8%) confirmed they had been diagnosed with neurofibromatosis type 2 (NF2).

All the patients except six (99.5%) answered the question about the tumor size at diagnosis. The self-reported tumor size at diagnosis was not known in 138 (10.6%) patients. Two hundred ninety-seven patients (22.9%) reported their tumor was 0 to 1 cm at the time of diagnosis, 373 (28.7%) patients

Table 1 Questions formulated regarding tumor size and symptomatology

Question	Possible answers
1. How big was your tumor (the largest or average measurement) at the time of diagnosis?	I do not know, 0–0.9 cm, 1–1.9 cm, 2–2.9 cm, 3–3.9 cm, over 4 cm
2. What was the primary symptom you experienced that prompted an evaluation that ultimately led to the diagnosis of your acoustic neuroma (please choose the most noticeable or most bothersome symptom that you experienced if more than one symptom was present)?	Hearing loss, tinnitus(ringing in the ear), facial twitching or paralysis, numbness in the face, dizziness, headaches, it was found "accidentally" when I received a computed tomography or magnetic resonance imaging for another reason

Table 2 Study population characteristics

Variable	Description
Sex	860 (66%) female, 444 (33%) male
Age at diagnosis	51.8 y (range: 8–86 y)
Source of population for questionnaire	Acoustic Neuroma Association 872 (66.9%), Mayo Clinic 432 (33.1%)
Time from diagnosis to questionnaire	5.5 y (range: 0–49 y)

Table 3 Main statistically significant results from the statistical analysis of the data

Variables, result	Test, *p* value
Self-reported tumor size and age at diagnosis, larger tumors in younger patients excluding NF2 (►**Fig. 2**)	ANOVA, $p < 0.001$
Giant tumors at diagnosis (larger than 4 cm) in younger patients excluding NF2 (42.4 ± 14.2 vs. 52.3 ± 12.1 y)	*t*-test, $p < 0.001$
Incidental diagnosis and year of diagnosis, increased incidental diagnosis after 2005 (5.7 vs. 11%)	Chi-square, $p = 0.022$
Age at diagnosis and birth date, patients with an earlier date of birth were diagnosed later in life	Pearson's correlation −0.826 $p < 0.001$
ANA vs. patients treated at our institution	
ANA, predominantly females (72.5 vs. 52.7%)	Chi-square $p < 0.001$
ANA, 2 y younger (51 ± 12.3 vs. 53 ± 13.9 y)	*t*-test $p < 0.001$

Abbreviation: ANA, acoustic neuroma association; ANOVA, analysis of variance; NF2, neurofibromatosis type 2.

reported tumor size of 1 to 2 cm, 266 (20.5%) patients reported tumors 2 to 3 cm, 130 (10%) had tumors 3 to 4 cm, and 94 (7.2%) patients reported their tumor was greater than 4 cm at the time of diagnosis (►**Fig. 1**).

Chief Complaint Leading to Diagnosis

One thousand one hundred and sixty-two patients provided a valid answer to the question regarding their primary symptom that led to diagnosis: hearing loss in 598 (51.5%), dizziness in 198 (17%), tinnitus in 130 (11.2%), facial numbness in 58 (5%), headache in 48 (4.1%), facial twitching/paralysis in 12 (1%), and incidental diagnosis in 118 (10.2%; ►**Fig. 2**). One hundred and forty-two patients were excluded from this analysis, including 124 (9.5%) who could not select the main symptom that led to diagnosis and checked multiple symptoms, 7 patients who did not respond, and 11 who provided an alternative free text

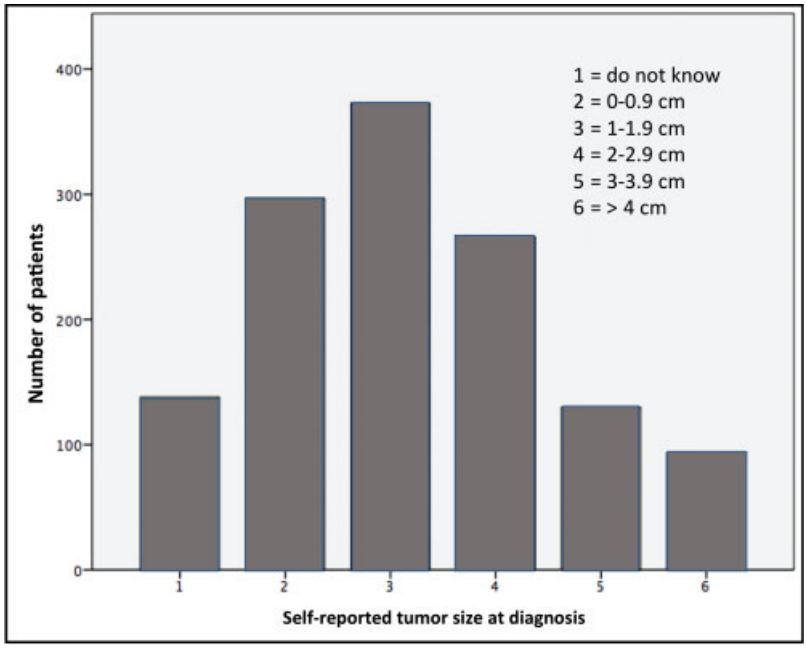

Fig. 1 Distribution of the reported tumor size at diagnosis in the patient series.

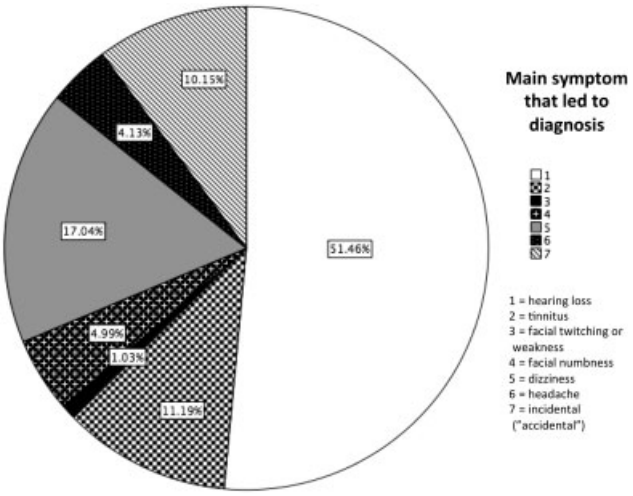

Fig. 2 Graphic illustrating the main symptom that led to diagnosis.

response (trigeminal neuralgia [$n = 5$], ear fullness [$n = 5$], and ear pain in [$n = 1$]). If the patients with NF2 are excluded from the analysis, the distribution of the main symptom at presentation does not suffer variations or is minimally altered: hearing loss in 51.5%, dizziness in 17.1%, tinnitus in 11.1%, facial numbness in 5.1%, headache in 4.1%, facial twitching/paralysis in 1%, and incidental diagnosis in 10.1%.

Incidental diagnosis was significantly associated with higher mean age at diagnosis (54.3 ± 12.8 vs. 51.4 ± 12.7 years, *t*-test, $p = 0.025$). Among symptomatic patients, patients with a chief complaint of dizziness were the oldest at diagnosis (mean, 53.2 ± 12.3 years) and patients with headache the youngest (mean, 43 ± 13.3 years; ANOVA, $p < 0.001$).

Self-Reported Tumor Size and Age at Diagnosis

Excluding NF2 patients, the younger patients had larger tumors than the older population. (ANOVA, $p < 0.001$) **(►Fig. 3)**. When comparing tumors greater than 4 cm with the rest of tumor sizes excluding NF2 patients, there was a statistically significant difference with a mean age at diagnosis of 52.3 years in tumors up to 4 cm versus 42.45 years in tumors larger than 4 cm (*t*-test, $p < 0.001$; **►Table 3**). The average age at diagnosis was significantly younger for NF2 patients as compared with sporadic tumors (*t*-test mean 43.9 vs. 52 years; $p = 0.004$).

Incidental Diagnosis and Year of Diagnosis

Incidental diagnosis comprised a significantly larger fraction of the overall VS population during the 10-year interval immediately preceding the study period (e.g., 2005–2015) than all preceding decades (Chi-square, $p = 0.02$). Incidental diagnosis was not related to sex, date of birth, age at diagnosis, or self-reported tumor size. However, patients with an earlier date of birth were significantly more likely to be diagnosed later in life (Pearson's correlation −0.826, $p < 0.001$).

ANA versus Patients Treated at Our Institution

As compared with our institutional cohort, subjects enrolled in this study through the ANA were significantly more likely to be female 72.5 versus 52.7% (Chi-square, $p < 0.001$). ANA patients were 2 years younger at diagnosis (*t*-test mean 51 vs. 53 years; $p < 0.001$). There was no significant difference in the proportion of NF2 patients between groups.

Discussion

VS is the most common cerebellopontine angle lesion, with an approximate incidence of 10 to 25 per million per year.[4,5,9] Interestingly, there has been a welldescribed upward trend in

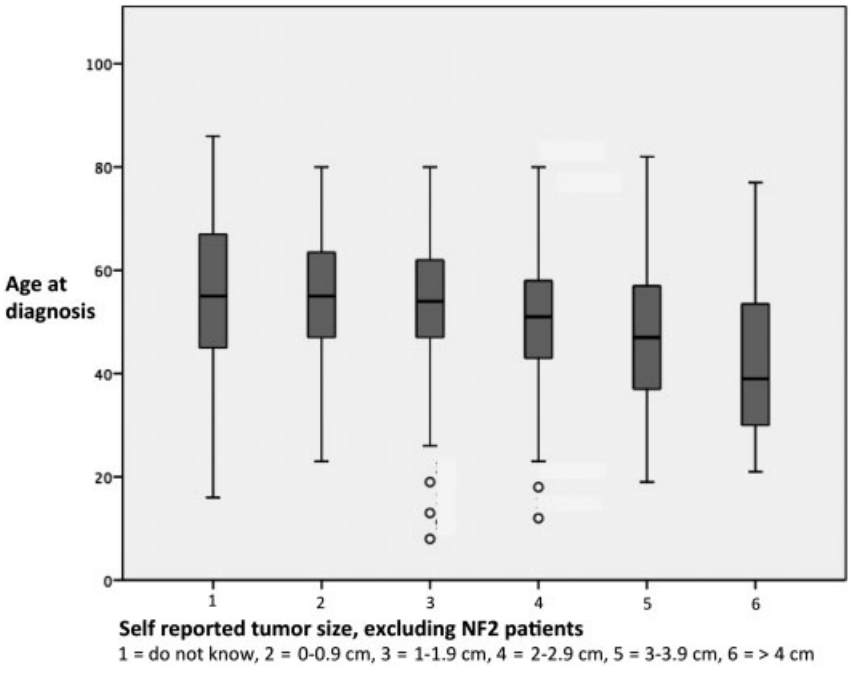

Fig. 3 Tumor size and age at diagnosis, the analysis shows that larger tumors are diagnosed at younger age.

the disease incidence, thought attributable to the increasing availability of imaging technology, in particular, magnetic resonance imaging (MRI).[10] To our knowledge, only a small number of prior publications have included more than 500 patients, the vast majority of which have captured a single institution's or surgeon's experience and clinical outcomes. Correspondingly, our analysis constitutes the first study that focuses on the aspects of clinical presentation defined by the patient's own experience.[11,12]

Ninety percent of patients were classified their tumor size at the time of diagnosis using the 1 cm size ranges defined by the questionnaire, or indicated that their tumors were larger than 4 cm. The analysis revealed that younger patients were diagnosed with larger tumors and tumors greater than 4 cm (giant VS) were diagnosed in patients who were a mean of 10 years younger than the rest of the VS population. This finding was reproduced when NF2 patients were excluded, an important consideration, given that these individuals are often the youngest to present, due to their frequently aggressive and multifocal disease.

Previous data regarding an association between age and VS size/growth rate are conflicting[2,13,14] and our results agree with a study by Matthies et al who also found that younger patients present with larger tumors.[2] Our present survey results are of course limited as results are based in self-reported data; however, our finding does strongly suggest that VS may be divisible into major phenotypic subgroups, such as large tumors in young patients who we suspect harbor more biologically aggressive lesions in spite of their otherwise common histology. This possibility highlights a critical area for future research, as discoveries in the underlying genetic, genomic, proteomic, or other molecular parameters of patients with dramatically different clinical phenotypes may reveal opportunities for earlier diagnosis, patients who would benefit from a more aggressive upfront resection strategy, or perhaps even niches where drug discovery research might eventually lead to medical interventions that will be incorporated into the treatment paradigm. In parallel, such advances may significantly benefit the NF2 population as well, an area of significant need given that their tumors develop remarkably early in life, as compared with those patients with sporadic VS.[15,16] Genetic studies performed in sporadic VS demonstrated that they are genetically heterogeneous although most of them had mutations in NF2 or in genes that could be linked to NF2.[17]

With respect to VS patients' chief complaints and the symptomatology driving presentation, it is particularly interesting that, when asked about the most prominent or "bothersome" symptom that led to diagnosis, only 51% referred to hearing loss as the main symptom, even though clinically significant hearing loss has been reported in the literature in 80 to 95% at the time of diagnosis.[1,3,7] These data are not conflicting as the patients in this study were specifically asked about the symptom that primarily made them seek medical attention, whereas previous studies identified clinical findings at the time of diagnosis. While hearing loss significantly affects quality of life and personal relationships, this discrepancy highlights how, the impact and implications of hearing loss may be substantially minimized by patients, who frequently do not come to medical attention until the deficit is severe, or another, more atypical symptom develops alongside hearing loss.[18] This is borne out in the high prevalence of dizziness, tinnitus, or headache, which account for more than one-third of the chief complaints that led to diagnosis. Based on our results, this difference appears to reflect an unanticipated expression of how patients experience VS symptoms, and what they respond to preoperatively as being their "most bothersome symptom." We acknowledge that NF2 patients may have differences in presentation but the NF2 population in this study is small so the percentages of the main symptom at presentation are mostly unaltered if we exclude them from the analysis.

Interestingly, although the second most prevalent presenting symptom reported in the preceding VS literature is tinnitus,[1] our survey places this classic disease feature third in importance, behind "dizziness" (e.g., vertigo). In so far as hearing loss is highly prevalent but apparently diminished in terms of patient-defined significance, dizziness is less commonly observed, but highly likely to drive clinical presentation where present. This accords with preceding findings in VS patient quality of life, including the results reported by Carlson et al, who identified dizziness, headache, and tinnitus respectively as the primary drivers in the decline in quality of life experienced by VS patients, compared with nontumor controls.[19,20]

Age also appears to play a role in how patients experience and respond to VS symptoms. More specifically, older patients frequently present with dizziness as their primary symptom, whereas patients who seek medical attention for headache are significantly more likely to be in the youngest age group. The former association may be attributable to the potentially multifactorial nature of dizziness in older patients, and the fact that imbalance becomes both commonplace and important among more elderly patients. Headache, by contrast, is likely associated with the large and presumably fast-growing tumors we identified as highly prevalent in younger patients, suggesting that his symptom arises from mass effect, hydrocephalus, or another driver of raised intracranial pressure (ICP). Alternatively, headache is more likely to present a major professional and personal obstacle in the lives of younger patients, and we speculate that they would therefore be more likely to rapidly pursue medical treatment for headaches that interfered substantially with quality of life, resulting in earlier diagnosis, even in those patients whose tumors were not necessarily the underlying cause of their headache. In a large series of objectively measured VS, tumor size did not correlate with symptoms,[21] whereas other large series report that larger tumors are associated with abnormal gait, headache, facial weakness, or numbness.[1]

Our study is subject to several significant limitations, the majority of which are derived from the reliance on self-reported, retrospective, survey-based data. This subjects our data to several sources of confounding as well as biases. The mean time from diagnosis to survey was 5.5 years with a wide range (range: 0–49 years), which may affect the results due to recall bias. The response rate is under 15% for the ANA patients and the response rate was not recorded for patients treated at our institution, which may be a source of inclusion bias. Whether the patients who answered the questionnaire had

more troublesome symptoms than the rest of the VS population, is not possible to prove or assess. Data on patient race and ethnicity could not be adequately captured and assessed within the parameters of our methodology, presenting another important limitation, given preceding reports suggesting possible differences in VS tumor behavior among major racial subgroups.[22] These limitations notwithstanding, given the large patient population the study included, and the simplicity of the methodology, we hold that our results provide a critical source of value data that has already identified multiple new avenues for exciting future studies. The present study is also tied to a patient advocacy group, the ANA which was created in 1981 to provide accurate patient information and to offer opportunities for positive interaction with other VS patients.[23] Although patient associations are useful research resources, providing information on a large and broad cohort of patients in a low-incidence diagnosis, they are not exempt from multiple sources of bias.[3,23–27] In our series, as compared with the institutional population, female patients and young patients were over-represented within the ANA cohort, a difference that we suspect is not clinically meaningful, particularly given the small size of the mean age difference (2 years). Intrinsic sources of bias such as patients' motivations, interests or clinical status when joining the ANA cannot be measured or assessed. In spite of these shortcomings, the ANA presents an excellent research resource, and multiple preceding publications have incorporated this population into a high quality analysis, particularly in the niches surrounding quality of life and symptomatology.[24,25]

Conclusion

In a large-scale, questionnaire-based review of 1,304 VS patients, we confirmed that clinical presentations are most frequently driven by hearing loss, followed by dizziness and tinnitus. Although these are the most prevalent symptoms in the overall VS population, the emphasis patients appear to place on symptoms other than hearing loss is interestingly elevated, and patients who are minimizing the importance of subtle unilateral hearing loss may highlight a candidate group for earlier diagnosis and intervention. Younger patients present with larger tumors, suggesting a biologically distinct tumor subtype that may represent phenotypically aggressive behavior, a critical area for future study. In addition to larger tumor size, headache and NF2 status were similarly prominent among younger patients. Unsurprisingly, 10% of tumors were discovered incidentally, an increasing number as access to MRI and other neuroimaging techniques continue to expanded remarkably.

Previous Presentation
Components of this work were submitted for presentation to the North American Skull Base Society Annual Meeting 2018.

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None.

Conflict(s) of Interest to Declare
None.

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