Review Article

Gradenigo's Syndrome: A Review

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Abstract

Background: Gradenigo's syndrome is an uncommon triad of retroorbital pain, diplopia due to 6th nerve palsy, and otorrhea due to otitis media and petrous apicitis. Although rarer in the antibiotic era, this syndrome may be life-threatening and highly morbid if not treated aggressively with IV antibiotics, and surgery in some cases. **Methods and Findings:** Herein we present a review of patients reported in the literature since 1990, with an exploration of medical vs. surgical treatment, causative organisms, and patient outcomes. Thirty-seven studies representing 38 patients were identified. The mortality rate was 2.6%, and the majority of patients were treated with either IV antibiotics alone (14) or IV antibiotics in addition to surgery (14). **Conclusions:** Prompt awareness of Gradenigo's syndrome can help avoid morbidity or mortality related to this uncommon phenomenon. It should be kept in the differential of any patient with otitis media, retroorbital pain, and diplopia.

Keywords: Gradenigo's syndrome; Systematic review; Petrositis; Abducens palsy

Introduction

Gradenigo first described the syndrome that bears his name in 1904 and later elaborated on the triad in 1907. [1,2] The triad classically consists of retroorbital or periauricular pain due to inflammation/irritation of the first (ophthalmic) division of the trigeminal nerve, diplopia due to inflammation of the abducens (6th cranial) nerve in Dorello's canal, and a draining ear due to a florid otitis media causing petrous apicitis. In the pre-antibiotic era, this condition was highly morbid and carried a high rate of mortality. Even in the antibiotic era, there are occasional reports of this serious condition. Petrous apicitis traditionally warranted surgical exploration to drain the infected middle ear, mastoid, and petrous apex, but with advances in imaging and antibiotic therapy, many patients can be managed conservatively with IV antibiotics, especially if the constellation of symptoms is recognized early. This article summarizes 37 studies published since 1990, encompassing 38 patients, and summarizes the medical and surgical management of Gradenigo's syndrome, comorbid conditions, patient demographics, and trends in management of this uncommon syndrome with a review of the literature.

Patients and Methods

A PubMed database search was performed using the keywords "Gradenigo syndrome". A total of 207 manuscripts were initially identified since 1990. After reviewing these articles, 85 were excluded as they were review articles or did not report data on patients with an actual diagnosis of Gradenigo's syndrome with the classically described Gradenigo's triad. An additional 85 of the remaining articles were excluded as they did not contain interpretable data or individual patient data that could be analyzed. Figure 1 illustrates the PRISMA flow chart for analysis and selection of the available articles. [3] The remaining 37 studies totaled 38 patients with individual data available. [4-40] Patient data was collected on age, sex, treatment modality (medical, surgical, or both), drugs used in treatment, sequelae of the disease, specific organisms isolated by culture, and any comorbidities present.

Results

Average patient age was 22.4 years (standard deviation=21 years). Of patients for who sex was reported there were 17 male patients and 17 female patients. Table 1 lists the data on patient age and sex. Four patients had neoplasms of the temporal bone that precipitated the Gradenigo's: one solitary osseous plasmacytoma, one embryonal rhabdomyosarcoma, one diffuse giant B-cell non-Hodgkin's lymphoma, and one well-differentiated nasopharyngeal squamous cell carcinoma. There was only one death reported, from brain abscess, giving a mortality rate of 2.6%. Two patients were reported to have bilateral Gradenigo's syndrome, and there was one pregnant patient reported. There was one HIV-positive patient reported, one patient with cavernous sinus thrombosis, and one patient with temporary ipsilateral facial weakness/facial nerve dysfunction. Of the patients for whom culture results were reported, four had negative cultures; one grew *Streptococcus intermedius*, one *Streptococcus pneumoniae*, one *Streptococcus acidominus*, one *Mycobacterium tuberculosis*, and one aspergillus. Table 2 summarizes the patient data on treatment modality. Fourteen patients were treated with IV antibiotics only, while another 14 were treated with IV antibiotics in addition to some form of surgery. One patient with a neoplasm was treated with radiation

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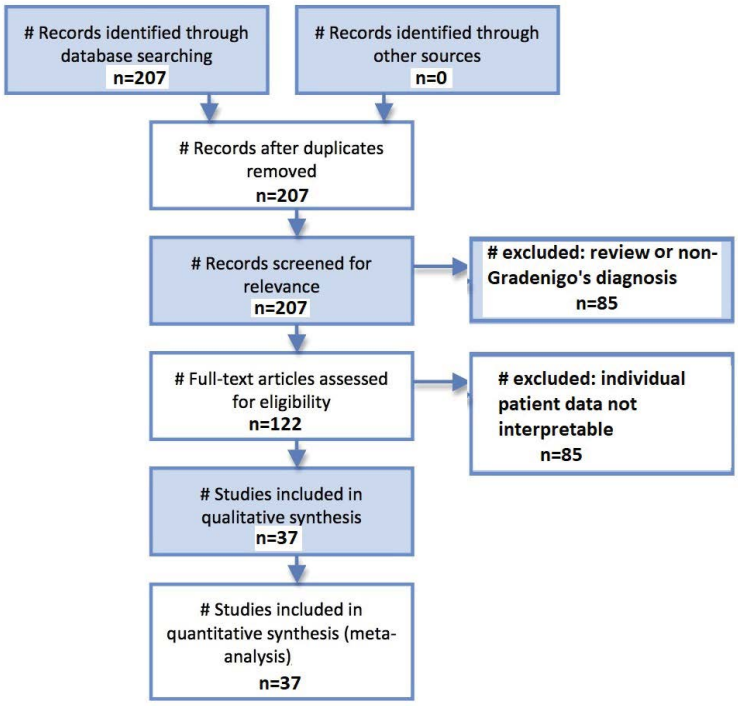

Figure 1: PRISMA flow diagram illustrating study selection.

treatment alone, while another patient with a neoplasm was treated with a craniotomy in addition to radiation therapy. Ceftriaxone was the most common IV antibiotic reported, with levofloxacin, metronidazole, ceftazidime, and clindamycin also utilized, typically in addition to ceftriaxone.

Discussion

In the post-antibiotic era Gradenigo's syndrome is rare but can still prove life-threatening and potentially morbid. In their recent 40-year series of 44 patients with petrous apicitis Gadre and Chole [41] noted that only six patients presented with the full classical Gradenigo's syndrome triad, and they noted a decreasing prevalence of patients needing surgery. They noted only one death in their series, consistent with the low mortality rate found in the present review. Kazemi [42] also recently reported on a young male adult patient with the classic Gradenigo's triad who responded dramatically to IV clindamycin and ceftazidime with resolution of all Gradenigo's symptoms by day four of antibiotic treatment.

Jensen [43] reported a retrospective series of four patients with Gradenigo's syndrome. In three patients the syndrome presented as the classic acute triad, but interestingly one patient presented with a delayed abducens nerve palsy relapse 6 years after the onset of chronic suppurative otitis media. Govea-Camacho and coworkers [44] reported a series of 5 patients aged 17–52 with complicated otitis media. Although several developed complications such as brain abscess, cavernous sinus thrombosis, meningitis, or Bezold abscess, none of the five developed the classic Gradenigo's triad.

Reddy and coworkers [45] published an in-depth exploration of the relationship between the work of Primo Dorello, Giuseppe Gradenigo, Wenzel Leopold Gruber, and Harris Holmes Vail and our current understanding of the relationship between Dorello's canal and the abducens nerve palsy seen in Gradenigo's syndrome. Gruber, an anatomist, was the first to describe Dorello's canal in 1859. Dorello's canal is a bony/fibrous conduit made by a depression near the petrous tip. It is located behind the petrosphenoidal ligament and lies between the apex of the petrous portion of the temporal bone and the clivus. The 6th cranial nerve passes through Dorello's canal while traveling through the petroclival region of the skull base. In 1904, Gradenigo first published descriptions of the triad of symptoms that bears his name: purulent and suppurative otitis media, retroorbital or periauricular pain due to trigeminal neuralgia, and palsy of the ipsilateral abducens nerve causing lateral rectus muscle paralysis. Gradenigo proposed that the mechanism of ipsilateral abducens nerve palsy was inward spread of the otitis media causing leptomeningeal inflammation that damaged the sixth cranial nerve, resulting in the abducens palsy. Primo Dorello published descriptions of the intracranial path of the abducens nerve. Dorello proposed that the abducens palsy seen in Gradenigo's syndrome was actually due to passage of middle ear infection through tympanic veins to the petrosal sinus, causing inflammation and compression of the 6th cranial nerve at the narrow, anatomically vulnerable Dorello's canal through which the abducens nerve passes on its way to innervate the lateral rectus muscle of the eye. This is consistent with the frequent resolution of the diplopia/lateral rectus paralysis once the concomitant apicitis/otitis media resolves and the localized compression of the abducens nerve is relieved. Later, in the 1920's, American physician Harris Holmes reported his observations regarding the anatomy of Dorello's canal in 8 specimens. He published the first English-language descriptions confirming Dorello's descriptions of the petrous

Table 1: Summary of age and sex data in patients with Gradenigo's syndrome.

Reference	Patient age (years)	Patient sex
Vitale	8	Male
Kazemi	33	Male
Jensen	9	Female
Ghani	7	Male
Karunakaran	13	Male
Janjua	10	Female
Lattanzi	60	Female
Valles	36	Female
Khalatbari	45	Male
Plodpai	63	Male
Choi	8	Female
Colpaert	12	Female
Bhatt	72	Male
Delgado	28	Female
Ricks	5	Male
Pedroso	33	Female
Fernández-Mayoralas	8	Female
Rossor	11	Female
Guedes	6	Male
Zengel	12	Male
Sethi	11	Unknown
Burston	6	Unknown
Burston	70	Male
Sherman	unknown	Male
Bloching	13	Female
Yozu	6	Female
Trimis	12	Female
Finkelstein	Unknown	Unknown
Penas-Prado	53	Male
Marianowski	6	Unknown
Minotti/Kountakis	Unknown	Female
Minotti/Kountakis	Unknown	Female
Hananya	5	Male
Dave'	4	Male
Morales	44	Male
Murakami	8	Female
Tutuncuoglu	13	Male
Hehl	30	Female

Table 2: Summary of treatment modalities in patients with Gradenigo's syndrome.

Treatment	Number of patients
IV antibiotics only	14/37
IV antibiotics + mastoidectomy	3/37
IV antibiotics + mastoidectomy + petrous apicectomy	2/37
Radiation therapy	1/37
IV antibiotics + mastoidectomy + craniotomy	2/37
IV antibiotics + tympanostomy tubes	6/37
Subtemporal/middle fossa craniotomy + radiation therapy	1/37

apex, petrosphenoidal ligament, and the path of the abducens nerve in relation to Dorello's canal. His descriptions were the first widely recognized anatomical studies to use the term "Dorello's canal" and Vail's work popularized the eponym used today. He reiterated that the anatomical location of Dorello's canal made the 6th nerve vulnerable to inflammatory swelling and compression in petrous apicitis/otitis media, producing the characteristic ipsilateral lateral rectus paralysis seen in Gradenigo's syndrome.

The present study demonstrated that patients with Gradenigo's syndrome tend to be young (average patient age=22.4 years in the present study), and male:female distribution is equal. The mortality rate was low, only 2.6%. Infection was the typical etiology but in rare cases malignancy of the temporal bone precipitated the infection leading to Gradenigo's syndrome. The causative organisms tended to be Streptococcus species, but also included more rare microbes such as aspergillus or *Mycobacterium tuberculosis*. Treatment was roughly evenly distributed between antibiotic treatment alone, and antibiotic treatment combined with surgical intervention. Fourteen of 37 patients were treated with IV antibiotics alone, with one patient with a temporal bone malignancy being treated with radiation therapy alone. The surgical treatments in addition to IV antibiotic therapy in the study ranged from simple tympanostomy tubes is six patients, to mastoidectomy alone in three patients, mastoidectomy combined with removal of the petrous apex bone in two, mastoidectomy combined with temporal craniotomy in two, and combined sub-temporal and middle fossa craniotomy along with post-operative radiation therapy in one patient. This demonstrates that the aggressiveness of surgical treatment should be tailored to the clinical course, comorbid or precipitating factors, and radiographic findings in each case. Gradenigo's syndrome should be kept in the differential for patients with otologic infections, particularly if 6th nerve palsy is present. Imaging with CT or MRI should be used to confirm the clinical findings and evaluate for associated malignancy or abscess, and aggressive IV antibiotic treatment combined with surgery when necessary should be implemented as soon as possible.

Conclusion

Though relatively rare in the post-antibiotic era, Gradenigo's syndrome can be highly morbid and even fatal if not recognized. Antibiotics remain the primary treatment modality, but surgery may be necessary in cases failing to respond to antibiotics or cases with associated skull base or intracranial abscess. In the present review, about 50% of the patients recovered with IV antibiotics alone, and most patients requiring surgery underwent tympanostomy tube insertion or mastoidectomy. Mortality was low and most patients recovered without sequelae. Gradenigo's should be kept in the differential for patients experiencing diplopia in the setting of facial/periauricular pain and otitis media.

Conflict of Interest

The authors disclose that they have no conflicts of interest.

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