

Research Article

Gradenigo Syndrome, Neurocysticercosis, Drug Therapy: Case Report and Systematic Review

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Abstract

Introduction: A quite rare and dangerous side effect of chronic otitis media is Gradenigo's Syndrome (GS). It is usually characterized by three symptoms: Ipsilateral abducens nerve palsy, which is caused by the spread of the infectious process from the middle ear to the petrous apex of the temporal bone; facial pain; and purulent otorrhea, which is usually caused by petrous apicitis as a consequence of acute otitis media.

Neurocysticercosis (NCC) is parasitic disease caused by the larva stage of the pig tapeworm *Taenia solium* when infect the brain, optic nerve and the spinal cord.

Methods: We searched the medical literature, following the guidelines outlined in the PRISMA statement. From 01st, January 1944 to 31st, January 2025, the authors searched the scientific databases, Scopus, Embase, Medline, and PubMed Central using the following searches: "Gradenigo's syndrome" OR "Petrous apicitis" OR "Otitis media complications" OR "Abducens nerve palsy" OR "Petrositis", OR "Cavernous sinus syndrome" OR "Trigeminal nerve" OR "Trigeminal neuralgia"

Results: After screening the full-text articles for relevance, 61 articles were included for final review. However, no article was found when we searched for GS/NCC/responding to drug therapy.

Conclusions: As far we know, this is the case report about comorbidity of NCC and GS. The association of GS and NCC is by coincidence and there not relationship between both pathogens. The local venous system plays an important role in the pathogenesis of GS complications. The broad-spectrum IV antibiotic is the treatment of choice.

Keywords: Gradenigo syndrome; Petrous apicitis; Otitis media complications; Retro-orbital pain; Mastoiditis; Skull base infections; Abducens nerve palsy; Petrositis

Introduction

A quite rare and dangerous side effect of chronic otitis media is Gradenigo's Syndrome (GS). It is usually characterized by three symptoms: Ipsilateral abducens nerve palsy, which is caused by the spread of the infectious process from the middle ear to the petrous apex of the temporal bone, causing inflammation and pressure on the abducens and some branches of the trigeminal nerves, primarily when the petrous apex is pneumatized; purulent otorrhea, which is usually caused by petrous apicitis as a consequence of acute otitis media; and facial pain [1]. Because the traditional triad is so rare, the diagnostic workup is difficult.

Recently, Ibrahim et al. found 80 cases of GS in 190 patients with a confirmed diagnosis of Petrous Apicitis (PA) and 10% of those patients were infected by *Fusobacterium necrophorum*. These authors established that it is brought on by an infection that spreads to the petrous apex of the temporal bone *via* the Dorello canal, impacting the trigeminal ganglion and abducens nerve (Meckel's cave). It causes ipsilateral abducens nerve palsy and excruciating pain when the first and second branches of the trigeminal nerve are irritated.

Italian otorhinolaryngologist Giuseppe Gradenigo documented this clinical experiment in 1904. He listed a number of symptoms, such as pain in the trigeminal nerve distribution, paralysis of the abducens nerve, and suppurative otitis media [2,3].

Meningoencephalitis, cerebral abscess, empyema, and

venous sinus thrombosis with compression of the nearby Internal Carotid Artery (ICA) resulting in cerebral infarction are among the consequences that can occasionally be observed [1]. In 1918, Gore MR established that the mortality rate was around 2.6% [4].

The most common microbial infections found in patients presenting PA/GS are *Pseudomonas* (37%) and *Staphylococcus aureus* (32%). Therefore, antipseudomonal and anti-staphylococcal antibiotics should be considered in these cases [1,5].

Petrous apicitis can be caused by several pathogens, including *Staphylococcus*, *Streptococcus pyogenes* and *Streptococcus pneumoniae*, while *Pseudomonas aeruginosa* is the most common. According to Tao et al., a case of pediatric Gradenigo syndrome was successfully treated with antibiotics that were suitably broad-spectrum. They described a 5-year-old who was not responding to ciprofloxacin-dexamethasone drops. Following successful treatment with empiric intravenous ceftazidime and cefazolin, he healed completely without the need for surgery after 16 weeks [5].

Taenia solium Taeniasis/Cysticercosis (TSTC) is a preventable foodborne, zoonotic, neglected tropical disorder predominately seen in persons living or visiting low and middle-income endemic countries. At the same time, Neurocysticercosis (NCC) is the consequence of invasion by the same cestode of the brain, optic nerves or the spinal cord which is identified as the larva form of the pig tapeworm *Taenia solium* (Ts). The most typical clinical features of this condition are Epilepsy (EP), Epileptic Seizures (ES) and headache, among other problems.

Pigs act as intermediate hosts of cysticercosis while humans are definitive hosts. Taeniasis, *i.e.*, intestinal infection with mature *T. solium* in the human host, occurs after ingesting undercooked pork meat infected with the larval stage (porcine cysticercosis). Cysticercosis in human beings occurs after humans ingest *T. solium* eggs or proglottids. NCC is the principal aetiology of secondary epilepsy in endemic areas [6-10]. ES and Ep are the most common symptoms of Cerebral Cysticercosis (CC). In the past, we performed more than a dozen epidemiological studies in rural areas around Mthatha, confirming that CC, also named Neurocysticercosis (NCC), is the primary aetiology of secondary epilepsy. Most ES and Ep respond well to first-line Antiepileptic Drugs (AED) and Antiseizure Medication (ASM) [11-20]. The most prescribe ASM is benzodiazepine, and the commonest used AED are valproic acid and carbamazepine [21-24].

This study's primary goal is to respond to the following research inquiries: How often is GS associated with NCC? What is the most likely relationship between GS and cavernous sinus syndrome?

Materials and Methods

Search strategy

From 01 January 1974 to 31 January 2025, we searched the

databases Embassy, Medline, Scopus, and PubMed Central using the following searches: "Gradenigo's syndrome" OR "Petrous apicitis" OR "Otitis media complications" OR "Abducens nerve palsy" OR "Petrositis", OR "Cavernous sinus syndrome" OR "Trigeminal nerve" OR "Trigeminal neuralgia". We searched the medical literature following the PRISMA guidelines. After removing duplicates, two reviewers (LDFIV and HFS) from each side screened titles and abstracts and evaluated the full texts of eligible articles based on the proposed inclusion criteria. Any disagreement between the reviewers involved in the literature search was resolved through discussion with all authors to reach a consensus.

Selection criteria

The following manuscripts were included in the systematic review:

Articles on Isaac syndrome, neuropathic pain, and Schwann cell disorder in ISA/NP, with detailed pathogenesis and/or drug therapy.

Exclusion criteria were as follows:

- Inaccessibility to full text.
- Articles with unclear pathogenesis.
- Lack of relevant clinicopathological data.
- Non-original studies (*i.e.*, editorials, letters, conference proceeding, book chapters).
- Animal model studies.
- Non-/Spanish/Portuguese/English studies. The papers were thoroughly assessed, and duplicates were looked for.

Data extraction and quality assessment

All selected data were tabulated in an electronic Excel database. That information included pathogenesis, drug management, initial clinical presentation, evaluation of NP/IS after treatment, follow-up, and status at the latest evaluation. The studies' quality was categorized as good, poor, fair, or reasonable, in agreement with the National Institutes of Health criteria. Two reviewers (LDFIV and HFS) independently evaluated the articles, and the discussion resolved disagreements.

Statistical analysis

The primary objective of this study was to evaluate whether DD's pathogenesis/drug management differs significantly among different therapies. Without a comprehensive reference for the total number of DD cases, the prevalence of DD responding to drug therapy with associated autonomic manifestations was searched through a comprehensive review.

Statistical analyses were performed using XLSTAT (add-on for Microsoft Excel, version 2021.4.1, Addinsoft SARL) and RStudio (version 4.3.1, <https://www.rstudio.com/>). Variations in continuous variables were assessed using the Mann-Whitney U-test. We presented descriptive statistics

for continuous variables as median (95% Confidence Interval (95% CI)). All situations were evaluated using the Kaplan-Meier method to identify relevant prognosticators. A model of multivariable Cox proportional hazards with a priori selection of covariates was used to check for independent prognostic effects.

Results and Discussion

A total of 514 titles were selected from the literature. After removing duplicates and excluding records, 61 relevant articles were examined. Twenty-three studies were unavailable for retrieval. After including six additional articles identified from citation searching, 43 were excluded for several reasons. A total of 61 records were identified from these searches. The resulting study titles were exported to Excel, and publications without including/excluding criteria duplicates were removed, leaving 22 unique titles. We screened all remaining unique full-text articles, abstracts, and titles for eligibility. Titles were typically excluded if unavailable in Spanish, Portuguese, or English or irrelevant to GS. Articles relevant to GS included the clinical presentation, management, treatment, and pathogenesis. The authors then screened these articles by abstract. After further review, abstracts were excluded if they were irrelevant to the topic, outdated, or unavailable in Spanish, Portuguese, or English. No articles were for full-text review because they did not report comorbidity of GS and NCC. Finally, when we searched for GS/NCC, no article was identified.

Series description and differences among groups

All the selected studies were relevant to the subject of this systematic review. None were randomized controlled trials or prospective studies; all the articles included were case reports and case series. The total number of patients presenting with documented GS/NCC was zero.

Median age was 14.7 (range 5–71) with significant differences between age groups ($p < 0.001$). We did not find remarkable variations in gender ($p = 0.064$), although males presenting GS were noticeably more frequent and slightly more prevalent.

A 39-year-old known chronic epileptic male patient secondary to calcified NCC well controlled under valproic acid 600 mg po twice a day over the past seven years. He came to the neurology OPD complaining of recurrent tonic-clonic generalized epileptic seizures for the past four days, with no response to the previous AED. He said that five days prior, he presented with severe generalized headache, left yellow-green-coloured otorrhea, facial pain, numbness, weakness of muscles of mastication, mild fever and otalgia. He attended the ENT clinic, where ciprofloxacin-dexamethasone ear ointment was prescribed.

However, the frequency of epileptic attacks increased, and the patient complained of horizontal binocular diplopia, worse on left gaze and excruciating left-side facial pain. He denied experiencing any recent trauma, tooth issues, or prior bouts of comparable symptoms.

On examination, he was fully alert and had typical vital signs. A left tympanic membrane perforation (anterior superior quadrant) with overt otorrhea, mild mastoid tenderness, and trace hearing reduction on the left side were confirmed. Neurological examination demonstrated left abducens nerve palsy. Given the severity of the symptoms, indications, and suspicion of an infectious process overlay, laboratory testing were conducted. The total blood count revealed a white blood cell count of 14,500/ μ L, which is within the reference range of 4,000–11,000/ μ L, indicating mild leucocytosis. The erythrocyte sedimentation rate was raised to 55 mm/h (reference range: 0–20 mm/h), and the C-reactive protein was raised to 35 mg/L (reference range: < 5 mg/L). An infection of the central nervous system was ruled out by the unremarkable results of the cerebrospinal fluid investigation. The microorganisms were confirmed by blood cultures, and broad-spectrum antibiotics were started right away.

Laboratory investigations exhibited a normal white blood count, marked platelet elevation ($691 \times 10^9/L$), and mildly raised C-reactive protein (12 mg/L). A rhinovirus/enterovirus swab was positive. Blood cultures were negative after 48 hours. However, the ear culture was found to be unprocessed after 3 days, as it was lost in transit to the laboratory. Repeat ear swabs and culture were negative after a further 48 hours.

Magnetic resonance confirmed bilateral multiple calcifications in the cerebral parenchymal involving the grey and White matter, clival osteomyelitis, otomastoiditis, and coalescent left petrous apicitis. Finally, there was asymmetric enhancement involving the left carotid canal with moderate narrowing of the left internal carotid artery without signs of cerebral venous sinus thrombosis.

To eradicate the bacterial pathogens causing mastoiditis and petrous apicitis, the patient was given intravenous ceftriaxone (2 g every 12 hours) and metronidazole (500 mg every 8 hours). To remove the purulent substance from the middle ear, a myringotomy was carried out after consulting with the otolaryngology specialists.

Comments and final remarks

All publications on Gradenigo syndrome, petrous apicitis, the number of cases reported with otitis media, their age and sex are included in Table 1, which is self-explanatory [25–86].

Table 1: A summary of the literature reviewed

First author	Year	PA cases	GS	OM	Age	Sex
Bridgewater [25]	1944	1	Yes	Yes	9	F
Ogilvie [26]	1945	2	Yes	Yes	10	F
			Yes	Yes	31	M

Horowitz [27]	1948	2	Yes	Yes	14	F
			Yes	Yes	30	F
Eby [28]	1961	3	Yes	Yes	21	M
			No	Yes	44	M
			Yes	Yes	38	F
Gillespie [29]	1962	1	Yes	—	—	—
Hiranandani [30]	1967	1	Yes	Yes	30	M
Horn [31]	1996	1	Yes	Yes	10	F
Murakami [32]	1996	1	Yes	Yes	8	F
Minotti [33]	1999	2	Yes	Yes	47	F
			Yes	Yes	36	F
Jagadeesan [34]	2002	1	Yes	Yes	4	F
Piron [35]	2003	1	Yes	Yes	5	F
Park [36]	2003	1	Yes	Yes	8	F
Finkelstein [37]	2003	1	Yes	Yes	12	M
Sethi [38]	2005	1	Yes	Yes	11	F
Visosky [39]	2006	4	Yes	Yes	8	M
			Yes	Yes	14	M
			No	Yes	66	F
			No	Yes	84	M
Hafidh [40] (NB: description of individual patients not provided)	2006	3	—	—	—	—
Rossor [41]	2011	1	Yes	Yes	11	F
Pollock [42] (NB: description of individual patients not provided)	2011	7	Yes	Yes	—	M=5, F=2
Kong [43]	2011	1	Yes	Yes	10	M
Jacobsen [44]	2012	1	Yes	Yes	3	M
Colpaert [45]	2013	1	Yes	Yes	12	F
Heshin-Benstein [46]	2013	2	Yes	Yes	3	M
			Yes	Yes	5	F
Chen [47]	2014	4	Yes	Yes	64	F
			Yes	Yes	33	F
			Yes	Yes	58	M
			Yes	Yes	45	M
Choi [48]	2014	1	Yes	Yes	8	F
Plodpai [49]	2014	1	Yes	Yes	63	M
Valles [50]	2014	1	Yes	Yes	36	F
Jensen [51]	2016	4	Yes	Yes	5	M
			Yes	Yes	46	F
			Yes	Yes	70	F
			Yes	Yes	13	M
Kazemi [52]	2017	1	Yes	Yes	33	M
Jensen [53]	2017	1	Yes	Yes	9	F
Vitale [54]	2017	1	Yes	Yes	8	F
Dorner [55]	2017	1	Yes	Yes	5	M
Taklalsingh [56]	2017	1	Yes	Yes	58	M
Ghani [57]	2017	1	Yes	Yes	7	M
Solms [58]	2017	1	Yes	Yes	10	M
Shapiro [59]	2017	1	Yes	Yes	11	F
Gadre [60] (NB: description of individual patients not provided)	2017	44	6 (13.6%)	27 (54.5%)	8–76 (Mean=39.2)	M=23, F=21
Brunet-Garcia [61]	2018	1	Yes	Yes	41	M
Al-juboori [62]	2018	1	Yes	Yes	61	M

Bozan [63]	2018	1	Yes	Yes	9	F
Özkaçmaz [64]	2019	1	Yes	Yes	14	F
Rossi [65]	2019	1	Yes	Yes	4	F
Athapathu [66]	2019	1	Yes	Yes	6	M
Brambilla [67]	2019	1	Yes	Yes	8	–
Savasta [68]	2019	1	Yes	Yes	11	M
McLaren [69]	2020	1	Yes	Yes	5	F
Patel [70]	2020	2	Yes	No	49	F
			No	Yes	46	M
Hodges [71]	2020	1	Yes	Yes	24	M
Demir [72]	2020	1	Yes	Yes	7	M
Chandran [73]	2020	2	Yes	Yes	54	F
			Yes	Yes	23	F
Guimaraes [74]	2021	1	Yes	Yes	63	F
Sattarova [75]	2021	1	Yes	Yes	65	M
Malic [76]	2021	1	Yes	Yes	5	F
Liu [77]	2021	1	Yes	Yes	35	F
Quesada [78]	2021	1	Yes	Yes	14	F
Bonavia [79]	2022	1	Yes	Yes	14	F
Jin [80]	2022	1	Yes	Yes	78	M
Chan [81]	2023	1	Yes	Yes	5	M
Brenda [5]	2024	1	Yes	Yes	5	M
Horache [82]	2024	1	Yes	Yes	15	M
Ali [83]	2024	1	Yes	Yes	38	F
Mammarella [84]	2024	1	Yes	Yes	71	M
Kim [85]	2024	1	Yes	Yes	11	M
Guenouni E [86]	2025	1	Yes	Yes	8	M

We did not find any reports on GS associated with NCC in our systematic review of the medical literature, probably because the comorbidity of GS and calcified NCC happens by coincidence only and GS is a very rare disorder despite that there is not a pathophysiological relationship between the *Taenia solium* and the bacterial infections causing OM and its complications, including GS. On the other hand, in South Africa, active NCC is already eradicated, although some patients presenting with epilepsy secondary to calcified NCC are still around seeking for medical attention [87].

To properly understand GS's pathophysiology, it is mandatory to be familiar with the most important aspects related to the affected cranial nerve in this syndrome. One of the most affected cranial nerves in GS is the Abducens Nerve (AN). At the pontomedullary junction, which is typically situated medially and caudally to the facial and

vestibulocochlear nerves, the AN fibers depart the brainstem after leaving the sixth nerve nucleus from the dorsal pons and ventral to the fourth ventricle. After passing through the SAS, the AN continues on toward the clivus, reaching the upper border of the petrous bone tip of the temporal bone. The nerve is particularly vulnerable to infection by the aforementioned bacteria, mastoiditis, otitis, and other conditions at this location of the petrous bone. Despite its location, the AN nerve is susceptible to stretching with changes in intracranial pressure in Dorello's canal, a fibrous boneless sheath that surrounds it after it passes the clivus. For this reason, abducens nerve palsy is not regarded as a localized neurological symptom. To innervate the lateral rectus muscle, AN leaves Dorello's canal, enters the CS, and then follows the ICA before entering the orbital cavity through the superior orbital fissure. The second one is the trigeminal nerve, responsible for the facial pain, as we report in our case and it's represented in Figure 1.

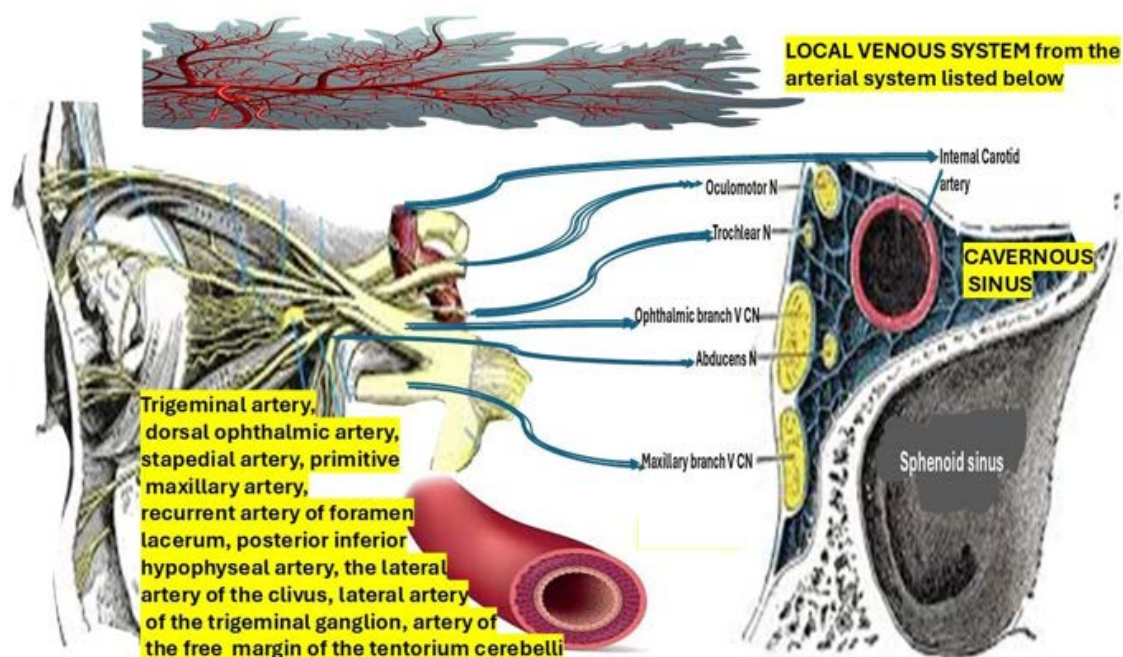


Figure 1: Anatomical illustration showing cranial nerves, arterial branches, and the cavernous sinus in relation to the sphenoid sinus and venous system

Brief comments on Cavernous Sinus (CS) syndrome as a complication of Gradenigo syndrome

The CS is a tripartite venous osteomeningeal compartment

that is adjacent to the internal carotid artery, the pituitary gland, the optic tracts, and cranial nerves III, IV, V, and VI (Figure 2).

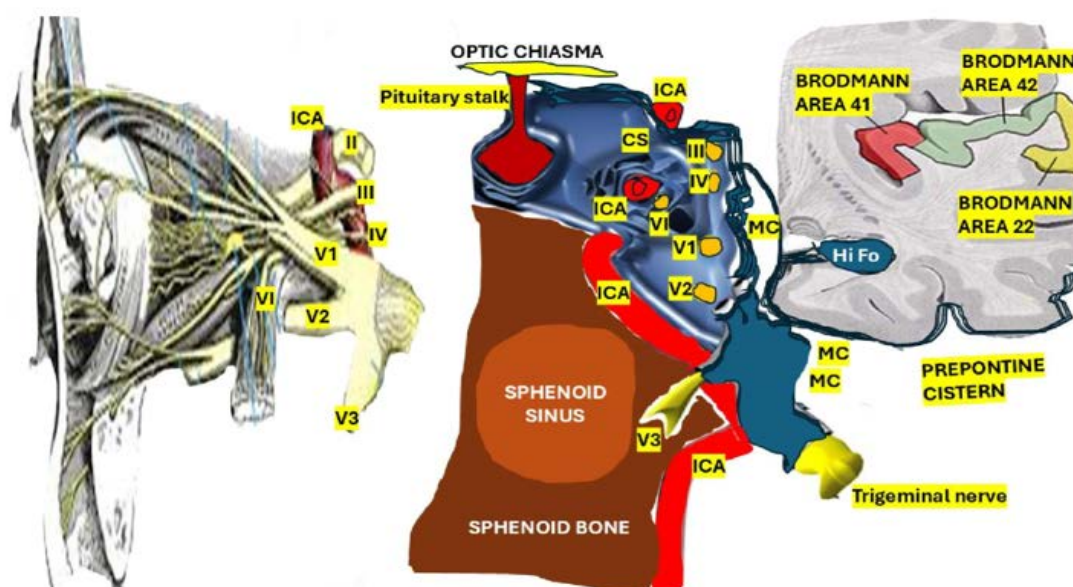


Figure 2: Illustration showing cranial nerves, internal carotid artery, sphenoid structures, and Brodmann areas in relation to the cavernous sinus

Drawing from research conducted by Lasjaunias and Moret et al. [88–90], we can emphasize that the Cavernous Sinus (CS) is supplied by four arteries: The trigeminal artery, the dorsal ophthalmic artery, the stapedia artery, and the primitive maxillary artery. Following birth, the CS is supplied by the posterior inferior hypophyseal artery, the

recurrent artery of foramen lacerum, the lateral artery of the clivus, also known as the dorsal meningeal artery, the lateral artery of the trigeminal ganglion, and the artery of the free margin of the tentorium cerebelli (Figure 1). On the other hand, the ocular globe and optic nerve are supplied by the dorsal

ophthalmic artery. The internal maxillary artery, maxillary-mandibular, and middle meningeal artery [91] will all get contributions from the stapelial artery. After the ocular division, the adult trigeminal artery leaves the basilar system and travels medially to the fifth cranial nerve before joining the internal carotid close to the carotid syphon in the CS. We hypothesized that some cases presenting CS syndrome can be explained by hematogenous spread of the infection through the trigeminal veins into the CS.

A proper understanding of the complexity of the CS's blood circulation will serve to comprehend better the pathophysiology of the CSS from GS hematogenous spreading complications.

The anatomical properties of the trigeminal (Gasserian) ganglion, which are dural and covered in a fine reticular membrane attendant to the branches that assist the clinical symptoms of face pain described in our case, led us to speculate that the GS's pathophysiology is influenced by

these features. The sympathetic plexus fibres passing from the ICA margin to the abducens nerve play an important role in this mechanism.

We hypothesized that the involvement of the local venous system (Figure 1) plays the principal role in the complication of GS presenting as CSS. The anterior/inferior compartment (below the intracavernous carotid, lateral to the clival region), the medial venous compartment (between the internal carotid and the pituitary), and the posterosuperior compartment (between the internal carotid artery and the posterior roof of the sinus) are the three local spaces surrounding the CS that are known to be susceptible to thrombophlebitis stemming from complicated GS.

We hypothesized that CSS might be a complication of sphenoid sinusitis (Figure 3) from a complicated GS by direct or hematogenous extension. The most common complications of GS are represented in Figure 3.

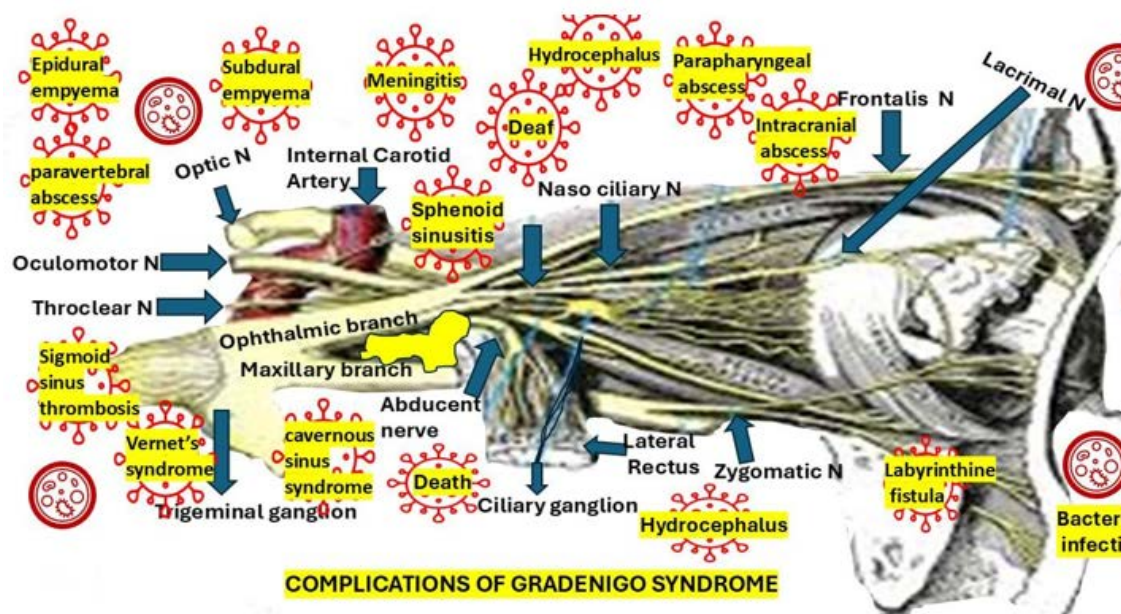


Figure 3: Anatomical depiction of Gradenigo syndrome showing cranial nerve involvement and severe complications such as meningitis, abscesses, and hydrocephalus

In our opinion, when there is a direct spread of the bacterial infection from GS through venous channels and/or damaged sinus wall of the CS, which can trigger the thrombus formation or thrombophlebitis, resulting in internal carotid artery vasospasm and extensive engorgement of the superior ophthalmic vein. We have theorized that the connecting venous vascular channels mainly contribute to the previously cited mechanism. Although it is not represented in Figure 1, we thought that the list of GS problems caused by bacterial migration into the CSF should include meningoencephalitis.

There are many stages of superior orbital fissure syndrome that can result from sphenoidal sinusitis, which is characterized by Horner's syndrome (mainly with myosis), proptosis, ophthalmoplegia, orbital cellulitis, facial pain

or hyperesthesia, and orbital apex syndrome involving the optic nerve, as has been reported by other authors [92].

Another anecdotal way of spreading bacterial infection from complicated GS is through the pterygoid plexus veins and pterygomaxillary space into the CS [93].

There is a natural mouth-shaped aperture within the petrous apex's meningeal dura propria and periosteal layers measuring 4×9 mm wide ant its opening and 15 mm in length in the medial portion of the middle cranial fossa known as Meckel's cave which conduit for the proximal rootlets of the trigeminal nerve, connects the CS to the prepontine cyst of the posterior fossa that house the Gasserian ganglion [94].

Several pathological conditions, such as inflammatory

processes, congenital disorders, infectious diseases, and vascular or neoplastic lesions, may involve Meckel's cave.

Brief comments on the infection causing GS and its drug therapy

Table 2: Differential diagnosis

Cholesteatoma, or implantation of epithelium by trauma to the tympanic membrane, can grow to a size that puts necrotic pressure on the petrous bone. Jackler RK, Parker DA. Radiographic Differential Diagnosis of Petrous Apex Lesions. The American Journal of Otology. 1992;13(6):562-573.
Tolossa-Hunt syndrome, Lemierre's syndrome. Kenza Horache, Manal Jidal, Ibtissam ElOuali, Rachida Saouab, Jamal Elfenni. Insights into Gradenigo syndrome: Case presentation and review. Radiol Case Rep. 2024 Sep 3;19(11):5442–5446.
Petrous effusion is fluid that drains into the air cells of the petrous temporal bone. This may be asymptomatic but can also form cysts. Jackler RK, Parker DA. Radiographic Differential Diagnosis of Petrous Apex Lesions. The American Journal of Otology. 1992;13(6):562-573.
Osteomyelitis may develop following chronic infection of the external ear, middle ear, mastoid, or petrous apex. Jackler RK, Parker DA. Radiographic Differential Diagnosis of Petrous Apex Lesions. The American Journal of Otology. 1992;13(6):562-573.
Neoplasms such as meningioma, intracranial plasmacytoma, chondroma and chondrosarcoma of the petrous temporal bone are very rare. Jackler RK, Parker DA. Radiographic Differential Diagnosis of Petrous Apex Lesions. The American Journal of Otology. 1992;13(6):562-573.
Cholesterol granuloma occurs when red blood cells and other tissue break down, releasing cholesterol to form crystals that induce an inflammatory response. These can form granulomas that destroy portions of the temporal bone. Jackler RK, Parker DA. Radiographic Differential Diagnosis of Petrous Apex Lesions. The American Journal of Otology. 1992;13(6):562-573

GS is a condition that can be caused by different types of bacterial infections, includes strains of *Pseudomonas aeruginosa* and *Streptococcus/Staphylococcus* [86]. There are several drug therapies able to control the most common bacterial infection leading to a petrous apicitis, such as ceftriaxone, vancomycin, metronidazole, benzylpenicillin, cefotaxime, clarithromycin, amoxicillin-clavulanate, and teicoplanin, despite none of them having reliable activity against *Pseudomonas aeruginosa*. Same authors have suggested that topical antibiotic therapies can be effective against *Pseudomonas aeruginosa*, but this drug therapy alone would not be sufficiently compelling to control intracranial infections [95].

Failure to properly treat GS may result in many complications as listed in Figure 2 or an inferior/fatal outcome. Therefore, we recommended a therapeutic program with sufficient coverage of all potential common pathogens, mainly non-confident culture studies or clinical evidence of skull-base involvement.

Other authors recommend administering intravenous antibiotics and anticoagulants, reporting radiological improvement and complete resolution of symptoms [82].

Other investigators prefer combining fluoroquinolones, vancomycin, and second or third-generation cephalosporins [96], only suggesting surgical debridement approaches for cases presenting osteomyelitis or abscess formation [97].

Notably, the petrous apex is close to important neurovascular systems, such as Meckel's Cave (MC) and the abducens nerve, contributes to the characteristic clinical features of GS, including facial pain, otalgia, and abducens nerve palsy [83]. It also makes it difficult to get a swift response to the drug therapy, mainly in cases of septic collection and dural enhancement around Meckel's cave, which will be documented below. Ali, et al. [83] also recommend requesting the otolaryngology team's support to perform a myringotomy to drain purulent material from the middle ear.

Before discussing about the aetiological infectious of GS, we like to mention the most relevant differential diagnosis of GS as it's listed in Table 2.

However, a 71-year-old man with a history of chronic otitis media and poorly managed type 2 diabetes mellitus presented with a GS by COM infection by *Pseudomonas aeruginosa* and delayed onset of abducens nerve palsy. He was treated with broad-spectrum antibiotics (IV beta-lactam) but showed no clinical improvement, according to Mammarella et al. [84].

In a 2022 systematic assessment of 134 PA patients, Talmor, et al. discovered that only 28 instances (20.9%) had the traditional GS triad of retro-orbital or facial discomfort, otorrhea, and abducens palsy [97,98]. These authors also found that *Klebsiella pneumoniae* is another pathogen frequently associated with GS, apart from two cases presenting tubercular petrositis, two infected by *Fusobacterium necrophorum*, two by *Candida parapsilosis* and one by nontuberculous Mycobacteria.

The many diagnostic classifications of GS, which are separated into three groups, do not correlate with the kind of infection or response to therapeutic drugs: PA, abducens nerve palsy, OM, and trigeminal nerve pain are signs of incomplete presentation; PA, abducens nerve palsy, and OM or trigeminal nerve pain are signs of mimic presentation; and PA, abducens nerve palsy, OM, and trigeminal nerve pain are signs of classic presentation. The diagnostic categories were proposed by McLaren and colleagues in 2020 [99].

Another reported case was treated with oral amoxicillin/clavulanate (Augmentin) with a good response. The same authors recommend similar broad-spectrum IV antibiotics, including cefotaxime, imipenem, ceftriaxone, or piperacillin/tazobactam, for at least 2-3 weeks. For patients presenting with an associated osteomyelitis, they suggest up to 6 weeks of treatment. They also recommend adding metronidazole to cover potential anaerobic organisms [85].

Patients not responding to drug therapy may present a spreading of the infection to nearby structures, leading to many types of complications, as we mentioned before,

includes Horner's syndrome-related extension to the sympathetic plexus and involvement of the jugular foramen [99].

The appropriate medication therapy for GS is still up for debate because of its rarity and clinical variability. Drug therapy is unquestionably important, but each case must be evaluated individually based on the patient's characteristics and the diagnostic category in order to determine the best course of action [100]. However, everybody agrees that broad-spectrum antibiotics are required to control infectious processes long-term (McLaren), primarily for all instances with abscesses that are situated in areas that are difficult to access surgically due to potential surgical complications or surgical limits [101-103].

The 8-year-old boy reported by Guennouni et al. [86] was infected by *Pseudomonas aeruginosa* and responded well to IV ciprofloxacin at 15 mg/kg/day for 2 weeks, followed by oral therapy. The same investigators recommend high-dose systemic and local antibiotic therapy, which should be extended over a prolonged period, even if there is a sustainable improvement after a shorter drug therapy.

Table 2 shows all differential diagnoses and conditions that might mimic GS without solely originating from PA; here, he only mentions those related to inflammations, prothrombotic states, and coagulopathies [82].

Conclusion

Finally, we conclude that, it is the first reported case about comorbidity of NCC and GS. The local venous system plays an important role in the pathogenesis of GS complications. The broad-spectrum IV antibiotic is the treatment of choice.

Author Contributions

Both investigators have read and agreed to the published version of the manuscript.

Conflict of Interest Statement

The authors declare they have no conflicts of interest.

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Ethics Statement

The study was conducted using the principles of the Helsinki Declaration, the Italian and US privacy and sensitive data laws, and the internal regulations for retrospective studies of the Otolaryngology Section at Padova University and Brescia University.

Informed Consent Statement

We obtained the informed consent from the case involved in the study.

Data Availability Statement

The corresponding author will make the raw data supporting this article's conclusions available upon request.

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