

2018

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This article was originally published as:

Lubomski, M., Dalglish, J., Lee, K., Damodaran, O., McKew, G., & Reddel, S. (2018). Actinomyces cavernous sinus infection: A case and systematic literature review. *Practical Neurology, Early View (Online First)*.

Original article available here:

<https://dx.doi.org/10.1136/practneurol-2017-001844>

This article is posted on ResearchOnline@ND at

https://researchonline.nd.edu.au/med_article/884. For more information, please contact researchonline@nd.edu.au.



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This is the author's version of the article published as:

Lubomski, M., Dalglish, J., Lee, K., Damodaran, O., McKew, G., and Reddel, S. (2018). *Actinomyces cavernous sinus infection: a case and systematic literature review. Practical Neurology*, Published Online First: 12 April 2018. doi: 10.1136/practneurol-2017-001844

Final published version available: <https://dx.doi.org/10.1136/practneurol-2017-001844>

MANUSCRIPT TITLE PAGE

Title:

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Word Counts

Abstract: 138
References: 17

Article: 1461
Figures: 2

Tables: 2

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Key Words: Actinomyces; Cavernous sinus; Ophthalmoplegia; Infection; Tolosa-Hunt syndrome

Title:

Actinomyces Cavernous sinus infection: a case and systematic literature review.

Abstract:

We report an unusual case of a 63-year old man who developed progressive right-sided exophthalmos, painful ophthalmoplegia, headaches and fevers with worsening depression over a two-month period, subsequently identified as an *Actinomyces* Cavernous sinus infection.

Subsequent diagnoses as more features developed were Giant Cell Arteritis then Tolosa-Hunt syndrome, with a transient response to steroids. A bland CSF and highly metabolically active brain FDG-PET suggested lymphoma. Biopsy of the mass demonstrated sulphur granules with Gram-positive filamentous bacteria with *Actinomyces*-like colonies.

Actinomyces cavernous sinus infections are rare and indolent. They often mimic non-infectious aetiologies including other inflammatory and infiltrative conditions, vascular and neoplastic causes, particularly lymphoma. Clinicians should consider infective cavernous sinus syndromes in fluctuating painful ophthalmoplegias with poor response to steroids. In our view, Tolosa-Hunt syndrome is a problematic term and should be retired or used only with reservation.

Introduction:

Actinomyces is a genus of slow growing filamentous anaerobic Gram-positive bacilli, commensals of the oropharynx, gastrointestinal tract, and urogenital tract (1). *Actinomyces* cavernous sinus infections causing painful ophthalmoplegia are rare, with only eight previous cases reported. Other Central Nervous System (CNS) *Actinomyces* infections may result in intra or extra axial abscess, meningitis, subdural empyema and actinomycoma. Trauma, dental infection, immunosuppression, malignancy and diabetes are risk factors for infection (1, 2). *Actinomyces* invasion of the cavernous sinus can cause painful ophthalmoplegia, which may be misdiagnosed as Tolosa-Hunt syndrome. Cavernous sinus infections often mimic malignancy, inflammatory disorders, lymphoma, meningioma, metastatic tumour or chronic granulomatous inflammation such as sarcoidosis or IgG4 disease (3, 4), Table 1. Other indolent infections that can cause skull base osteomyelitis include *Aspergillosis*, *Mucormycosis*, *Streptococcus spp.*, *Staphylococcus spp.*, Gram-negative bacilli, anaerobes and mycobacterium (5). We report an unusual presentation of bilateral cavernous sinus *Actinomyces* infection causing right-sided painful ophthalmoplegia, in addition to providing a review of literature of prior cases.

Clinical Summary:

A 63-year-old man developed progressive right-sided retro-orbital headache, worsening depression, then painful ophthalmoplegia with later ptosis and exophthalmos, then fevers over a two-month period. Shortly after the onset of his headache, he had an MRI brain without contrast, with no abnormality identified including on retrospective review. Treatment elsewhere with corticosteroids for presumed Giant Cell Arteritis then for Tolosa-Hunt syndrome achieved a transient response. Two-months after onset, our examination demonstrated right exophthalmos, global ophthalmoplegia, chemosis, ptosis and hypoaesthesia in the ophthalmic nerve (CN:V-1). Visual function and fields were normal with mildly reduced acuity bilaterally (6/12-2 OU) secondary to cataracts. Molar dental extractions were performed four-months previously due to caries, however no dental abscess or osteomyelitis was noted.

Acute investigations included leucocytosis $16 \times 10^9/L$ (4-10), C-reactive protein: 44mg/L (<5) and erythrocyte sedimentation rate: 81mm/hr (<14). CT and repeat MRI brain/orbits

demonstrated a granular enhancing mass centred at the right cavernous sinus, extending into the right orbital apex and superior orbital fissure, encasing the right internal carotid artery (Figure 1: A,B,C,D). Brain Positron Emission Tomography (PET) demonstrated markedly increased glucose metabolism (19.7 MBq) favouring a high-grade malignancy such as lymphoma. CSF examination was surprisingly bland with one mononuclear cell, no organisms, normal protein: 0.31g/L (0.15-0.45), glucose, cytology and flow cytometry.

An urgent cavernous sinus biopsy was performed. The surgical finding showed an inflammatory mass with sulphur granules and organisms seen on frozen section. The pathological findings were active inflammation with neutrophilic infiltrate consistent with abscess formation and Gram-positive filamentous bacteria with *Actinomyces*-like colonies forming macroscopic sulphur granules (Figure 2: A,B). No organisms were grown on culture. 16S rRNA molecular analysis was inconclusive due to mixed sequences, raising the possibility of polymicrobial infection.

Treatment included six-weeks of IV benzylpenicillin, followed by one-year of oral amoxicillin. His headaches and depression receded within weeks of therapy. A progress MRI brain at six-months showed significant reduction in the size of the enhancing lesion in the right cavernous sinus. Examination at six-months showed only mild right CN:V-1 hypoaesthesia and subtle right-sided ptosis.

Discussion:

The diagnosis of an *Actinomyces* cavernous sinus infection is challenging due to clinician unfamiliarity with atypical organisms, its rarity and indolent presentation. Actinomycomas appear on imaging as mass lesions, in contrast to many other infective processes, which often appear as destructive lesions or abscesses. The differential of subacute painful ophthalmoplegia and its clinical features are presented in Table 1. The definition of Tolosa-Hunt syndrome is unilateral orbital pain associated with paresis of one or more of the IIIrd, IVth and/or VIth cranial nerves caused by a granulomatous inflammation in the cavernous sinus (6). In Australia and UK where we have practiced, Tolosa-Hunt syndrome is used for painful ophthalmoplegia, with or without MRI changes, without pathology, with a dramatic improvement in swelling and pain shortly upon initiation of steroids.

The danger in regarding Tolosa-Hunt syndrome as a diagnosis, and not a syndromic eponym for a range of specific disorders of the orbital apex of varying severity, has long been recognized (7). Nonetheless this term as a diagnosis has persisted despite improvements in imaging and recognition of entities such as IgG4 disease, lymphoma and chronic infections, which may have misleading initial responses to corticosteroids. In our view, the technical ICHD definition of Tolosa-Hunt syndrome implies biopsy to establish a granulomatous condition, in which case granulomatous conditions: sarcoidosis, ANCA associated, IgG4 disease, specific infection, or other final cause should be given as the diagnosis. However, in practice biopsy is rarely done before a trial of steroids and invoking Tolosa-Hunt syndrome. Tolosa-Hunt syndrome should not be used as a diagnosis but either retired or merely used with reservation for syndromes that resolve with treatment without a precise diagnosis. We would prefer a simple description: painful ophthalmoplegia resolving with corticosteroids, which naturally implies uncertainty and a need for careful review. Moreover, where an imaging lesion is seen, biopsy should proceed unless there are cogent contraindications, given the potential for delayed/misdiagnosis and difficulties in chronic immunosuppression of an uncertain pathogenesis.

A systematic review of all-prior reported cases of *Actinomyces* causing ophthalmoplegia, (Table 2) (5, 8-14), identified three out of eight reports, plus our patient, initially misdiagnosed as Tolosa-Hunt syndrome. Empirical steroid treatment often clouds the diagnosis of CNS infection by transiently improving systemic features and occasionally focal neurological signs but later acceleration of the infection (12-14). The source of cavernous sinus infection is often uncertain however five reports suspected dental caries. Across all reports the prodromal symptoms were headache, painful ophthalmoplegia with complete or isolated cranial nerve palsies, occasionally with exophthalmos. These symptoms were indolent with one to seven-months progression, leading clinicians away from infection. Seven out of eight reports described fevers, but intermittent or late in the disease course. All obtained biopsies to confirm the diagnosis. Where lumbar punctures were performed, an inflammatory and cellular CSF was suggestive, predominantly with neutrophilic infiltrate. However, our case demonstrates that CSF is not necessarily abnormal, and with the abnormal FDG-PET scan favoured a lymphoma as the pre-biopsy diagnosis, while recognising the differential of an indolent infection.

No prior reports were able to grow *Actinomyces* from CSF cultures or visualize microorganisms. CNS abscesses typically arise from haematogenously spread odontogenic biofilms, which are more often polymicrobial in nature. In our study we were unable to identify *Actinomyces* from 16S rRNA amplification due to a poor quality mixed read, potentially reflecting polymicrobial infection. *Actinomyces* infections are often polymicrobial as tissue invasion via mucosal surfaces may be accompanied by other commensal bacteria, which help facilitate infection by creating a microaerophilic environment (2, 9, 15). All eight prior reports described successful treatment with penicillin between two to six-months duration. All made a reportedly full recovery although our patient had minimal residual, with no relapse, despite other literature suggesting that >50% of CNS *Actinomyces* infections have residual neurological sequelae (2, 8).

MRI imaging is most appropriate for visualizing the cavernous sinus, for diagnosis and therapeutic response (16). Gadolinium administration preferably with fat suppression is useful in defining the infiltrative extent through the cavernous sinus and surrounding structures including the orbital apex and parasellar areas. MRI Angiography is helpful to evaluate for potential erosion, compression or thrombosis of the internal carotid artery (16). This case is noteworthy for a good quality MRI brain albeit without contrast earlier in the symptom course showed no abnormality of the cavernous sinus, even upon retrospective review. It should also be recognized that high FDG-PET uptake values, as identified in our case, can still represent infection and are not specific for malignancy (17).

We report a rare presentation of bilateral cavernous sinus *Actinomyces* infection causing painful right-sided ophthalmoplegia with exophthalmos with preserved visual acuity, histopathologically identified from a cavernous sinus biopsy with a good clinical recovery treated with penicillin. To our understanding only eight prior cases have been previously reported, all diagnosed from tissue biopsies, treated with penicillin with favourable outcomes. Our report demonstrates the importance of obtaining a biopsy to confirm the diagnosis. Indolent cavernous sinus infections present significant diagnostic challenges to clinicians. They often mimic non-infectious aetiologies, are mislabelled as Tolosa-Hunt syndrome, and may fluctuate or initially respond to corticosteroids. Cavernous sinus infections should be suspected earlier and investigated thoroughly including biopsy, when response to empiric

treatments is incomplete or refractory.

No acknowledgements

Conflicts of Interest and Disclosures:

All authors declare no financial or other conflicts of interest.

Key Points:

- *Actinomyces* cavernous sinus infections are rare and often mimic other inflammatory and infiltrative conditions, vascular and neoplastic causes, particularly lymphoma.
- Infective cavernous sinus syndromes are often mislabelled as Tolosa-Hunt syndrome due to clinical fluctuation and an often-initial partial response to steroids.
- Brain MRI imaging may lag clinical disease progression and should be performed with contrast.
- Where a cavernous sinus lesion can be demonstrated on imaging, biopsy should be the standard of care when response to empiric treatments is incomplete or refractory.

Figure Legends:

Figure 1:

A Axial CT non-contrast. **B** Axial T1 MRI with Gadolinium (Gd). **C and D** Coronal T1 MRI with Gd. The images demonstrate a granular, enhancing mass centered at the right cavernous sinus, 3.5cm x 2.5cm x 1.6cm extending into the sella, left cavernous sinus, right middle cranial fossa, anteriorly into the orbital apex and superior orbital fissure. The mass encases the right internal carotid artery, which is narrowed (**B, D**).

Figure 2:

A Hematoxylin and eosin stain x100 magnification. **B** Gram Stain x 600 magnification. Active inflammation with a neutrophilic infiltrate consistent with abscess formation (**A**, arrows), there are Gram-positive filamentous bacteria (**B**, arrows, dark filaments bottom & right) consistent with Actinomyces-like colonies. Macroscopically these clumped colonies appear as sulphur granules prior to staining.

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