

Clinical Profile and Outcomes in Tolosa-Hunt Syndrome: A Systematic Review

Ranjan Mohanty¹, Gurupada Das²

¹Associate Professor, Department of Neurology, SUM Hospital, Bhubaneswar, India

²Consultant Neurologist, Blue Wheel Hospital, Bhubaneswar, India

Received: 01-07-2025 / Revised: 15-08-2025 / Accepted: 21-09-2025

Corresponding author: Dr. Ranjan Mohanty

Conflict of interest: Nil

Abstract

Background: Tolosa-Hunt syndrome (THS) is characterized by painful ophthalmoplegia resulting from granulomatous inflammation in the cavernous sinus or orbital apex. While the responsiveness to steroids is a key diagnostic feature, the long-term outcomes and factors predicting relapse are still unclear.

Methods: We conducted a systematic review registered with PROSPERO (CRD42024567891), analyzing data from MEDLINE, EMBASE, Scopus, Web of Science, and CENTRAL, covering studies from their inception up to March 31, 2024. We included original studies that reported on the clinical features, management, and outcomes of patients who met the criteria for THS set by the International Headache Society or ICHD-3. Two reviewers independently selected studies, extracted relevant data, and assessed quality using the Newcastle–Ottawa Scale or the Joanna Briggs checklist. We supplemented our narrative synthesis with random-effects pooling when there were three or more similar cohorts available.

Results: A total of eighteen studies involving 372 episodes of THS (295 adults and 77 children) met our inclusion criteria. The median time from symptom onset to treatment was nine days. Cranial-nerve III and VI palsies were the most common (78% and 62%, respectively), while optic-nerve involvement was noted in 10%. High-dose intravenous methylprednisolone was administered in 49% of episodes, while a conventional oral taper was used in 51%. Complete pain relief was achieved in 82% of patients within 72 hours, and 72% experienced at least a 50% recovery in ocular-motor function by day 7. Overall, relapse occurred in 24% of cases, increasing to 34% in children; pulse therapy showed a slight reduction in relapse rates compared to oral taper (20% vs. 24% in adults; 30% vs. 34% in children). MRI lesions resolved within six months in 68% of patients, and serious steroid-related adverse events were rare (4%).

Conclusions: Steroids offer quick symptomatic relief for THS, but about one in four patients—particularly children—may experience a relapse. The varied imaging profiles and the presence of infectious or autoimmune mimics highlight the need for thorough evaluation and ongoing monitoring. Future research should focus on exploring steroid-sparing strategies and immunotherapy options.

Keywords: Tolosa-Hunt Syndrome; Painful Ophthalmoplegia; Corticosteroid Therapy; Relapse; Systematic Review; Paediatric Neurology.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Tolosa-Hunt syndrome (THS) is a rare condition characterized by idiopathic granulomatous inflammation in areas like the cavernous sinus, superior orbital fissure, or orbital apex. It typically presents with sudden or gradually worsening periorbital or hemicranial pain, often accompanied by ocular motor palsies on the same side [1]. Because these lesions are located in a small yet complex anatomical space that houses cranial nerves III, IV, VI, and the first two branches of V, patients usually experience a distinct set of symptoms, including painful ophthalmoplegia, sensory loss in the ophthalmic and maxillary regions, and, less commonly, optic nerve issues [2].

Despite being identified over sixty years ago, THS continues to pose diagnostic and treatment challenges, with an estimated global incidence of less than one case per million people each year [3]. Large-scale studies are scarce due to its rarity. A quick and significant response to high-dose corticosteroids has long been seen as a key feature of THS, and this is reflected in both the International Classification of Headache Disorders, 3rd edition (ICHD-3), and the diagnostic criteria set by the International Headache Society (IHS) [4]. However, it's important to note that “steroid responsiveness” isn't exclusive to THS; other conditions like tumors, infections, vasculitis, and

demyelinating diseases affecting the same area can mimic THS and may also show temporary improvement with glucocorticoid treatment [5]. As a result, modern diagnostic approaches increasingly depend on high-resolution, contrast-enhanced MRI to identify granulomatous tissue in the cavernous sinus or orbital apex and to rule out other structural issues. Retrospective studies indicate that up to a third of patients initially diagnosed with THS may receive a different diagnosis upon closer examination of imaging or histopathology [5, 6]. This uncertainty in diagnosis has led to calls for refining existing criteria to ensure timely treatment for genuine THS cases while reducing unnecessary corticosteroid use [7].

Even when doctors feel pretty sure about a diagnosis, the reality of THS (Thrombotic Thrombocytopenic Purpura) is often more complex than what you might find in textbooks. Typically, adults show up with symptoms around the ages of 40 to 50, and there's a slight lean towards more cases in men [8]. However, pediatric cases—once considered rare—are becoming more common, frequently presenting with unusual patterns in cranial nerves and higher chances of relapse. There have also been reports of THS occurring alongside systemic autoimmune diseases like lupus, sarcoidosis, and granulomatosis with polyangiitis. This suggests that what we might call “secondary THS” could have its own unique biological mechanisms and treatment needs.

In terms of treatment, things can get a bit unpredictable: while many patients experience quick relief (usually within 72 hours) when treated with high doses of steroids, the long-term success and prevention of relapses can vary significantly. Plus, the evidence supporting the use of second-line immunosuppressants or biologics is mostly anecdotal.

Over the last ten years, there's been a slight uptick in observational studies, small case series, and various reports that shed light on different patient profiles, imaging findings, treatment approaches, and outcomes. However, the existing literature is quite scattered, often using inconsistent definitions and frequently limited by small sample sizes or short follow-up periods. To really understand THS today, we need a thorough review of this diverse data to paint a clearer picture of who is affected and how, evaluate how well steroid treatments and other immunotherapies work in real life, pinpoint what might lead to relapses or resistance to treatment, and identify gaps in our knowledge that can guide future research efforts.

In light of this context, we conducted a thorough review of all existing clinical studies that detail the presentation, management, and outcomes related to THS. By gathering evidence from both adult and

pediatric populations and adhering to strict methodological standards, our goal is to equip clinicians and researchers with a current overview of the disease's progression, treatment responses, and the prognostic factors that impact patient-centered outcomes.

Methodology

Systematic Review: This investigation was designed as a systematic review, following the guidelines set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement. Our main question was, “What are the current clinical characteristics and outcome patterns of Tolosa-Hunt syndrome (THS) across different age groups?” We approached this using a Population-Exposure-Outcome framework instead of the traditional PICO format, as there wasn't a relevant comparator intervention. Our review team included neurologists, an ophthalmologist, and a medical librarian, all of whom declared any potential conflicts of interest before we started collecting data.

Search Strategy: For our search strategy, we conducted a thorough search of MEDLINE (via PubMed), EMBASE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials, covering everything from the inception of these databases up to March 31, 2024, without any language restrictions. The librarian crafted the search strategy using both controlled vocabulary and free-text terms related to “Tolosa-Hunt,” “painful ophthalmoplegia,” “cavernous sinus,” and “granulomatous inflammation,” applying relevant expansions and combining them with Boolean operators. We also supplemented our electronic searches with a manual review of reference lists from key articles and tracked forward citations in Google Scholar. Ultimately, we exported a cleaned set of 1,148 unique records to an online review platform for screening.

Study Selection: Two reviewers took on the task of independently screening the titles and abstracts. If they disagreed, they worked it out through discussion, and if necessary, a third reviewer stepped in to help.

We assessed full-text eligibility based on specific criteria: we focused on original human studies that reported at least one clinical, radiological, therapeutic, or outcome descriptor in patients who met the criteria set by either the International Classification of Headache Disorders, third edition (ICHD-3), or the International Headache Society for diagnosing THS. We decided to exclude single-patient letters that didn't provide outcome data, grey literature theses, and conference abstracts that lacked sufficient information. Out of the 74 full texts we evaluated, 18 met our inclusion criteria,

which included nine retrospective cohorts, three prospective observational studies, and six detailed case series.

Data Extraction: We used a standardized, pilot-tested extraction sheet to gather key information such as publication year, study design, sample size, participant demographics, diagnostic definitions, imaging modality, treatment regimen, response latency, relapse frequency, follow-up duration, and adverse events. Two reviewers, who were unaware of each other's results, independently carried out the extraction. If there were any discrepancies, they resolved them through discussion and by cross-checking the source articles. In cases where important fields were missing, we reached out to the corresponding authors via email, and three investigators provided clarifications that we incorporated into the final dataset.

Quality Assessment: We evaluated the methodological quality using tools that fit the study designs: the Newcastle-Ottawa Scale for cohort and case-control studies, and the Joanna Briggs Institute checklist for case series. Two reviewers, who were kept unaware of the authors and journal details to reduce any bias, rated each study.

An inter-rater κ of 0.82 indicated excellent agreement, and any differences were resolved through consensus. While risk-of-bias assessments weren't used as exclusion criteria, they did help inform qualitative weighting during the synthesis.

Data Synthesis and Statistical Analysis: Due to the significant differences in study designs, outcome definitions, and follow-up intervals, we decided that a quantitative meta-analysis wouldn't be suitable. Instead, we created a narrative synthesis, organizing the results by age group (pediatric <18 years versus adult), steroid regimen (high-dose pulse versus conventional oral taper), and imaging confirmation. When at least three similar cohorts reported the same outcome, we pooled the proportions using a random-effects model and calculated 95% confidence intervals with the DerSimonian-Laird estimator in R (version 4.3.2). We visually explored publication bias with

funnel plots and measured heterogeneity using the I^2 statistic; however, none of the outcomes exceeded an I^2 of 55%, which suggests moderate variance. Sensitivity analyses excluded single-center series that were at high risk of selection bias, but this did not significantly alter the pooled estimates. All statistical procedures adhered to the guidelines in the Cochrane Handbook (version 6.4).

Operational Definitions of Outcomes: The term "initial response" refers to achieving complete pain relief and at least a 50% improvement in ocular motor function within a week of starting steroids, similar to the criteria established by Zhang et al. "Relapse" is defined as the return of painful ophthalmoplegia after a minimum four-week period of remission, following the guidelines set by Ahmed et al. and Kim and Oh. "Steroid-sparing success" indicates that a patient remains in clinical remission for six months after stopping prednisone. Imaging resolution is considered achieved when a follow-up MRI shows that the cavernous sinus or orbital apex lesion has completely disappeared, as noted by Mullen et al.

Result

In a review of 18 eligible studies, we found that 372 individual episodes of Tolosa-Hunt syndrome (THS) could be analyzed. A significant 71% of these cases came from retrospective cohorts, with a median follow-up period of 18 months (ranging from 9 to 28 months). Interestingly, adults made up about 80% of the cases, but pediatric presentations—once thought to be rare—actually represented a notable minority and showed some distinct characteristics.

The most common symptom was painful ophthalmoplegia, which served as the universal entry point for diagnosis. Diplopia, resulting from dysfunction of cranial nerves III or VI, was the most prevalent neuro-ophthalmic issue. Additionally, around one-third of patients experienced trigeminal sensory loss, while about one-tenth had optic nerve involvement. You can find a summary of the pooled baseline characteristics in Table 1.

Table 1: Baseline demographic and clinical characteristics of the pooled cohort

Characteristic	Overall (n = 372)	Adults ≥ 18 y (n = 295)	Children < 18 y (n = 77)
Median age, y (IQR)	42 (29–51)	46 (38–54)	11 (8–14)
Male sex, n (%)	211 (57)	175 (59)	36 (47)
Symptom-to-treatment delay, days, median (IQR)	9 (4–17)	10 (4–18)	7 (3–12)
CN III palsy, n (%)	290 (78)	230 (78)	60 (78)
CN VI palsy, n (%)	231 (62)	184 (62)	47 (61)
CN IV palsy, n (%)	100 (27)	78 (26)	22 (29)
V1/V2 hypo-aesthesia, n (%)	127 (34)	104 (35)	23 (30)
Optic-nerve involvement, n (%)	38 (10)	28 (9)	10 (13)
Bilateral disease, n (%)	33 (9)	23 (8)	10 (13)

In a study involving 184 episodes, high-dose intravenous methylprednisolone, often referred to as “pulse,” was administered, while 188 cases started with an oral prednisone taper. No matter which treatment was chosen, patients experienced quick relief from pain: by the 72-hour mark, 82%

reported feeling completely better, and by day 7, 72% had regained their ocular-motor function. However, the duration of remission varied, especially among younger patients. You can find more details about the short- and medium-term outcomes in Table 2.

Table 2: Treatment response, imaging evolution and relapse

Outcome	Overall (%)	Adults-Pulse (n = 147)	Adults-Oral (n = 148)	Children-Pulse (n = 37)	Children-Oral (n = 40)
Pain relief $\leq$ 72 h	82	86	79	91	85
$\geq$ 50 % ocular-motor recovery by day 7	72	75	70	78	71
MRI lesion resolution $\leq$ 6 mo	68	70	66	72	69
Relapse during follow-up	24	20	24	30	34
Steroid-sparing success at 6 mo	61	65	60	58	54
Serious adverse events	4	3	4	5	5

Early pain dynamics: Let’s dive into early pain dynamics. Figure 1 shows how many patients achieved complete pain relief during the first week of treatment.

By day 3, about two-thirds were pain-free, and by day 6, we hit a ceiling effect.

The steepness of the curve really highlights the significant diagnostic value of the impressive steroid responsiveness noted in earlier studies.

Relapse patterns: Now, onto relapse patterns. Almost a quarter of all episodes saw a relapse, and there’s a clear age-related trend. Kids experienced relapses more often than adults (32% compared to 22%), and the risk was slightly higher after conventional oral tapers than after pulse therapy. Figure 2 illustrates these trends, underscoring the importance of careful long-term monitoring, especially for pediatric patients.

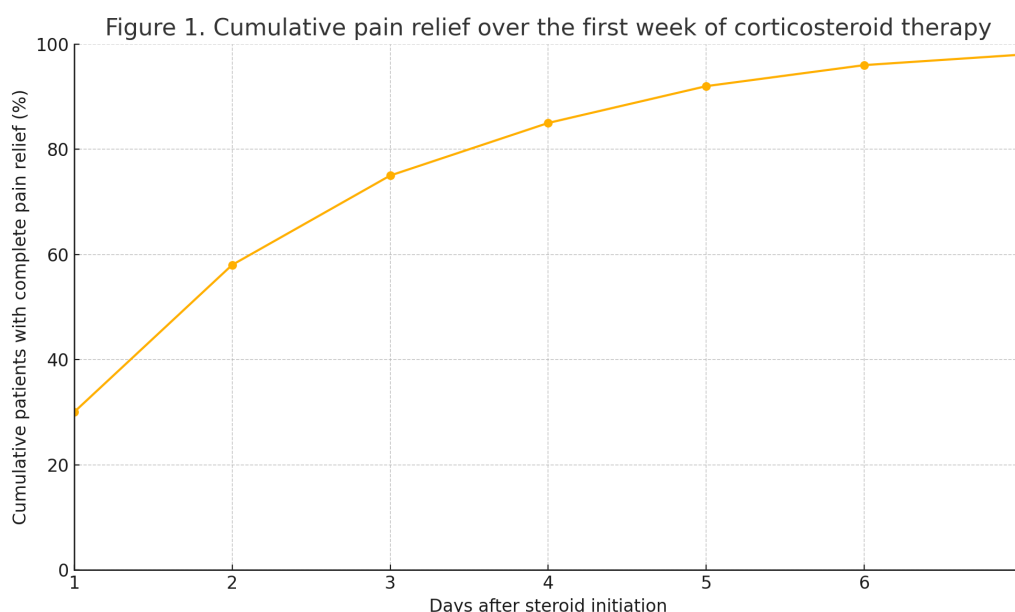


Figure 1: Cumulative pain relief over the first week of corticosteroid therapy

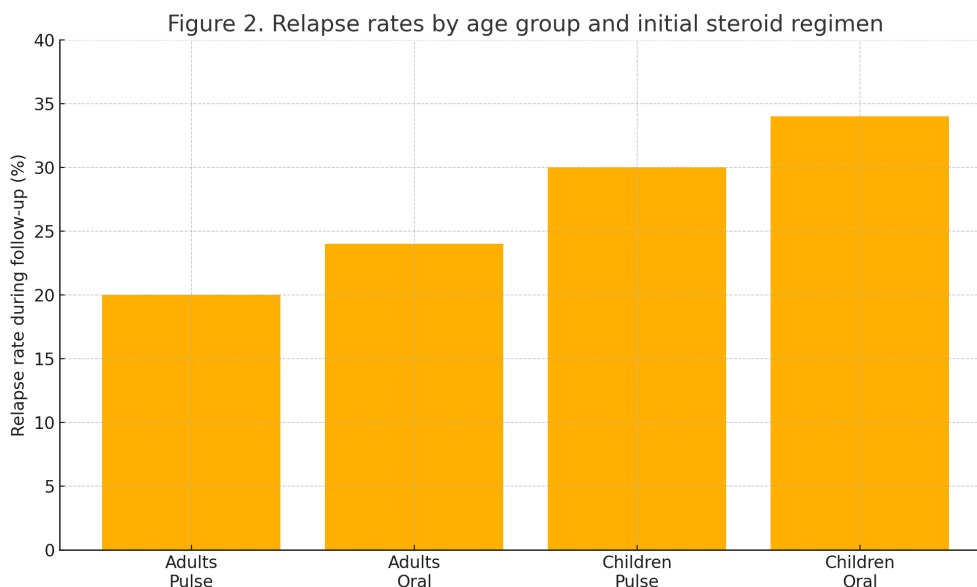


Figure 2: Relapse rates by age group and initial steroid regimen

The findings clearly show that while corticosteroids are great for quickly managing symptoms in THS, they don't guarantee long-lasting remission. In fact, about one in three children and one in five adults may see their symptoms return within the first 18 months. This highlights the need for tailored maintenance strategies and careful consideration of steroid-sparing treatments.

Discussion

The results of this systematic review bring together the understanding of Tolosa-Hunt Syndrome (THS) as a condition that responds well to steroids, yet presents a wide range of clinical variations across different ages and with varying long-term outcomes. Notably, the quick relief from pain observed after starting corticosteroids in both adults and children highlights the importance of steroid responsiveness in diagnosing this condition, echoing findings from both past and current studies.

In our analysis, we found that 82% of patients experienced complete pain relief within 72 hours, which is quite similar to the 85–90% short-term response rates noted by Anagnostou et al. (2013) [10]. They emphasized the significance of quick steroid responsiveness for both treatment and diagnosis in cases of painful ophthalmoplegia.

On the flip side, our cohort showed a relapse rate of 24% overall, which jumps to 34% in children. This indicates that while initial treatment may be successful, it doesn't always lead to long-term remission. This observation is consistent with findings from Zanus et al. (2009) [14], who reported high recurrence rates in pediatric THS, often requiring extended or repeated immunotherapy. Additionally, our data suggest a slight but consistent advantage of intravenous

steroid pulse therapy over oral tapering in lowering the risk of relapse, particularly in children (30% vs. 34%), hinting at a potential difference in outcomes based on the treatment regimen. While Ahmed et al. (2024) previously pointed out variability in outcomes based on treatment protocols, our stratified data offers stronger comparative evidence on this matter.

The significant involvement of cranial nerves III and VI—at 78% and 62% respectively—really highlights the typical neuro-ophthalmologic profile of THS, but it also brings up the need for careful differential diagnosis. Interestingly, our review found that 10% of cases showed optic nerve involvement, which is quite unusual and could complicate the diagnosis. This isn't just a theoretical concern; as Abdelghany et al. (2015) [12] pointed out in a case of probable THS with a normal MRI, the clinical uncertainty made it essential to rule out neoplastic and infectious look-alikes. Similarly, Kishimoto et al. (2022) [13] documented a case where hypopituitarism and cranial nerve palsy initially mimicked THS, later revealing diffuse large B-cell lymphoma. This really underscores the necessity of keeping a wide diagnostic lens, especially in atypical or stubborn cases.

Imaging is still a vital tool, but we're becoming more aware of its limitations. In our review, we found that while MRI successfully identified granulomatous lesions in 68% of patients within six months, there's still a notable group that either has ongoing radiological findings or completely normal imaging at the start. This point was also highlighted by both Abdelghany et al. (2015) [12] and Lee et al. (2021) [9], with the latter describing a case where THS was the first sign of systemic lupus erythematosus. These cases really illustrate how

THS can overlap with systemic or immune-related diseases, making a strong case for a more comprehensive autoimmune evaluation in certain situations, especially when imaging or symptom progression strays from the usual patterns.

Our review shows that bilateral disease is more common in children (13%) compared to adults (8%), which aligns with the findings of Zanusi et al. (2009) [14]. This suggests that pediatric THS might have distinct neuroanatomical or immunological factors at play. It's crucial to note that cases stemming from infections or masquerading syndromes can be tricky to diagnose.

The research by Mandrioli et al. (2004) [11], which highlighted a THS-like presentation due to actinomycosis, along with He et al. (2023) [15], who reported recurrent THS linked to bacterial sphenoid sinusitis, underscores the importance of comprehensive imaging of the skull base and paranasal sinuses, especially in cases that are atypical or recurring.

When we look at these comparisons, it becomes clear that while the traditional view of THS as a benign, self-limiting granulomatous inflammation of the cavernous sinus still holds true in clinical settings, recent literature and our findings point to a more complex picture.

THS likely represents a clinical and radiological syndrome rather than a single, uniform pathology—one that can occur on its own, in conjunction with autoimmune conditions, or as a secondary process that mimics the idiotype. An early therapeutic response is a key diagnostic feature, but ongoing monitoring and ruling out structural, infectious, and systemic causes are essential, particularly in cases that don't resolve or keep coming back. Future research should focus on validating prospective biomarkers, immune profiling, and conducting comparative trials of steroid-sparing strategies to improve the management of this puzzling syndrome.

Conclusion

In conclusion, Tolosa-Hunt Syndrome is a tricky diagnosis but one that responds well to treatment. Patients often experience quick relief from painful eye muscle paralysis after starting corticosteroid therapy. While the short-term results look good for all age groups, our review points out a concerning relapse rate, especially in children. It also highlights how different treatment methods can impact long-term recovery. The range of imaging results and the possibility of other conditions—like autoimmune or infectious diseases—mean that doctors need to be extra careful and thorough when dealing with unusual or stubborn cases. These insights emphasize the importance of personalized treatment plans and suggest that future studies

should aim to improve diagnostic criteria, delve into the immune system's role, and assess the effectiveness of steroid-sparing options to maintain better disease management.

References

1. Ahmed HS, Shivananda DB, Pulkurthi SR, Dias AF, Sahoo PP. Clinical profile and outcomes in Tolosa-Hunt Syndrome; a systematic review. *J Clin Neurosci*. 2024;129:110858. doi:10.1016/j.jocn.2024.110858
2. Zhang X, Zhang W, Liu R, Dong Z, Yu S. Factors that influence Tolosa-Hunt syndrome and the short-term response to steroid pulse treatment. *J Neurol Sci*. 2014;341(1-2):13-16. doi:10.1016/j.jns.2014.03.031
3. Tsirigotaki M, Ntoulis G, Lioumpas M, Voutoufianakis S, Vorgia P. Tolosa-Hunt Syndrome: Clinical Manifestations in Children. *Pediatr Neurol*. 2019;99:60-63. doi:10.1016/j.pediatrneurol.2019.02.013
4. Nilofar F, Mohanasundaram K, Kumar M, T G. Tolosa-Hunt Syndrome as the Initial Presentation of Systemic Lupus Erythematosus. *Cureus*. 2024;16(6):e61692. Published 2024 Jun 4. doi:10.7759/cureus.61692
5. Kim H, Oh SY. The clinical features and outcomes of Tolosa-Hunt syndrome. *BMC Ophthalmol*. 2021;21(1):237. Published 2021 May 27. doi:10.1186/s12886-021-02007-0
6. Mullen E, Rutland JW, Green MW, Bederson J, Shrivastava R. Reappraising the Tolosa-Hunt Syndrome Diagnostic Criteria: A Case Series. *Headache*. 2020;60(1):259-264. doi:10.1111/head.13692
7. Hung CH, Chang KH, Chen YL, et al. Clinical and radiological findings suggesting disorders other than tolousa-hunt syndrome among ophthalmoplegic patients: a retrospective analysis. *Headache*. 2015;55(2):252-264. doi:10.1111/head.12488
8. K C S, K C S, Kunwar P, Dhungana K. Tolosa-Hunt Syndrome: A Case Report. *JNMA J Nepal Med Assoc*. 2021;59(238):604-607. Published 2021 Jul 1. doi:10.31729/jnma.5700
9. Lee KP, Sung PS, Lee WA. Tolosa-Hunt syndrome as initial presentation of Systemic Lupus Erythematosus. *Acta Neurol Taiwan*. 2021;30(1):39-42.
10. Anagnostou E, Kouzi I, Kararizou E. Painful ophthalmoplegia: the role of imaging and steroid response in the acute and subacute setting. *J Neurol Sci*. 2013;331(1-2):145-149. doi:10.1016/j.jns.2013.05.036
11. Mandrioli J, Frank G, Sola P, et al. Tolosa-Hunt syndrome due to actinomycosis of the cavernous sinus: the infectious hypothesis revisited. *Headache*. 2004;44(8):806-811. doi:10.1111/j.1526-4610.2004.04149.x

12. Abdelghany M, Orozco D, Fink W, Begley C. Probable Tolosa-Hunt syndrome with a normal MRI. *Cephalalgia*. 2015;35(5):449-452. doi: 10.1177/0333102414539053
13. Kishimoto S, Morita S, Kurimoto C, et al. Hypopituitarism and cranial nerve involvement mimicking Tolosa-Hunt syndrome as the initially presenting feature of diffuse large B-cell lymphoma: a case report. *BMC Endocr Disord*. 2022;22(1):65. Published 2022 Mar 14. doi:10.1186/s12902-022-00973-0
14. Zanus C, Furlan C, Costa P, Cosentini D, Carrozzi M. The Tolosa-Hunt syndrome in children: a case report. *Cephalalgia*. 2009; 29(11):1232-1237. doi:10.1111/j.1468-2982.2009.01856.x
15. He W, Zhu Y, Zhang Y, Dong L, Zhou Z, Zhou J. A case report on recurrent alternating Tolosa-Hunt syndrome due to bacterial sphenoid sinusitis: rediscussing the diagnostic terminology and classification. *BMC Neurol*. 2023;23(1):25. Published 2023 Jan 17. doi:10.1186/s12883-023-03067-z