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Full Length Article

The visual outcome and efficacy of current therapies for neurosarcoidosis with anterior visual pathway involvement: A systemic review

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ABSTRACT

Purpose: To examine the clinical characteristics of neurosarcoidosis with anterior visual pathway involvement (NSAVP), assess the effectiveness of current treatments, and provide insights into the demographics, symptoms, and treatment outcomes to better guide clinical management of NSAVP.

Methods: The databases PubMed, Embase, MEDLINE, CINAHL and Ovid were searched to identify relevant studies. Statistical analyses were performed in R.

Results: Thirty-three studies involving 334 patients and 404 eyes were included in the meta-analysis. Our findings indicate that NSAVP predominantly affects females. Bilateral involvement was observed in 46 % of cases. Visual loss was the most common presenting symptom, affecting 94 % of patients; 78 % had no prior symptoms of systemic involvement. Three percent had isolated AVP manifestations. Fewer than 17 % had co-existing orbital or cranial nerve signs and 29 % had co-existing uveitis.

Sixty-three percent had an MRI abnormality of the AVP. The most frequently reported laboratory abnormality was an elevated white cell count in cerebrospinal fluid (CSF), followed by elevated protein in CSF and elevated serum ACE level.

Following treatment, 57 % experienced visual improvement. The visual improvement rate was similar for patients receiving steroids alone (46 %) and those receiving combined steroid and immunosuppressive therapy (44 %). Combined therapy was associated with a lower the incidence of no light perception (NLP, 1 % vs. 16 %), a higher proportion with vision better than 20/200 (70 % vs. 62 %) and a lower incidence of relapse (16 % vs. 40 %).

Conclusion: NSAVP predominantly affects females, with visual loss being the most common presenting symptom. Combination therapy of steroids and immunosuppressants was associated with better outcomes than steroids alone, including lower incidence of relapse and fewer cases of no light perception.

1. Introduction

Sarcoidosis is an inflammatory disease with multi-system involvement and is characterized by the development of noncaseating granulomas in various tissues. Involvement of the central nervous system (CNS) by sarcoidosis, a condition referred to as neurosarcoidosis, is rare, accounting for 5 % to 15 % of sarcoidosis patients (Cacao et al., 2017). While ocular involvement occurs in 25 % to 60 % of all sarcoidosis cases (Yates et al., 2022) anterior visual pathway (AVP) involvement is less common, accounting for only 6.4 % of neurosarcoidosis cases. This can lead to significant visual impairment, ranging from 20/40 to light perception (Arun et al., 2020; Kidd et al., 2016). For example, as high as

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24 % of patients with AVP sarcoidosis are reported to have a final visual acuity worse than 20/200 (Webb et al., 2021). Challenges in early detection and diagnosis may delay treatment and contribute to sight loss, making research into AVP involvement in sarcoidosis essential to improve outcomes and quality of life.

However, the rarity of AVP involvement in neurosarcoidosis has limited research primarily to retrospective cohort studies and case reports, with no controlled clinical trials to date (Cremers et al., 2013). Current treatment relies primarily on systemic corticosteroids which may be associated with a high failure rate when used alone (Arun and Palace, 2021). Alternative treatments, including immunosuppressive agents such as methotrexate, azathioprine, and mycophenolate mofetil, have improved outcomes by managing chronic inflammation. Additionally, anti-TNF-α agents such as infliximab and adalimumab (Fritz et al., 2020), as well as anti-CD20 monoclonal antibodies (Henderson et al., 2021), have shown promise in treating refractory or progressive cases.

Diagnosing AVP involvement in neurosarcoidosis is challenging due to its heterogeneous presentations (Koczman et al., 2008). Symptoms can range from transient or progressive visual loss to a complete lack of symptoms (Kidd et al., 2016). The absence of specific diagnostic biomarkers and the difficulty in obtaining CNS biopsies, particularly from the anterior visual pathway, often delay diagnosis and treatment.

There is a lack of systematic reviews addressing the diagnostic and treatment challenges of anterior visual pathway (AVP) involvement in neurosarcoidosis and the largest English-language multi-centre cohort study included only 35 patients.

Our study aims to bridge this gap by comparing visual outcomes in patients treated with traditional corticosteroids versus those receiving second- and third-line therapies. This analysis will serve as a valuable reference for ophthalmologists and neurologists, helping to guide clinical management and identify areas for future research.

2. Material and methods

2.1. Protocol and registration

Our study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) ensuring rigorous standards in our review process (Supplemental Digital Content 1). It is registered with PROSPERO (CRD42023422194) and was conducted in accordance with the ethical principles of the Declaration of Helsinki.

2.2. Eligibility criteria

2.2.1. Inclusion criteria

(1) Population: Adults (≥18 years) with suspected sarcoidosis, confirmed either through biopsy showing noncaseating granulomatous inflammation or by meeting the highly probable or probable criteria set by the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) (Judson et al., 2014) when other diagnoses are excluded. Cases identified as possible neurosarcoidosis in studies were confirmed by two researchers (X.Z. and T.A.) to prior to inclusion.
(2) Anterior Visual Pathway Involvement: defined by one or more of the following: (a) radiology (MRI or CT) confirmed optic neuritis, optic perineuritis, compressive optic nerve neuropathy, or optic granuloma; (b) radiology confirmed inflammation, infiltration or compressive neuropathy involving the optic chiasm; (c) fundus examination or OCT confirmed optic disc swelling or optic disc granuloma; (d) clinical signs consistent with possible optic neuritis according to the 2022 Lancet Neurology classifications (Petzold et al., 2022).
(3) Outcomes: At least one of the following outcomes was reported: (a) treatments; (b) visual outcomes before or after treatment; (c) the number of relapses; (d) MRI progression;
(4) Study Design: (1) prospective or retrospective cohort studies or case series with more than three subjects meeting our criteria; (2) full text available;

2.2.2. Exclusion criteria

(1) Patients aged under 18, or those with visual impairment due to posterior visual pathway pathology, or without clear evidence of anterior visual pathway involvement.
(2) Studies that do not differentiate between definite, probable, or possible neurosarcoidosis.
(3) Duplicate case reports from the same institution(s), unless otherwise confirmed by the corresponding authors.
(4) Literature reviews, editorials, conference abstracts, technical notes, and studies involving non-human subjects; and duplicate publications.

2.3. Information sources and search strategy

We searched databases including Ovid MEDLINE, Ovid Embase, PubMed, Web of Science, and CINAHL from January 1900 to December 2024, with no language restrictions. Searches were updated before the final analysis, and were focused only on human studies. The strategy is detailed in Supplementary Table 1. References of all included studies were manually searched to further identify additional related studies.

2.4. Study selection and data extraction

Study Selection: Duplicate publications were identified and removed using RAYYAN software, followed by independent title and abstract screening by researchers (X.Z. and B.C.) to select studies meeting our criteria. Full texts were then reviewed for eligibility. Any disagreements at this stage were discussed, and a third reviewer (L.L.) was consulted if consensus could not be reached.

Data Handling for Overlapping Studies: Special attention was given to studies with overlapping cohorts, particularly those originating from the same institutions. When overlaps in inclusion periods were detected, we assessed whether the data might bias the overall results. In such cases, two studies from the Wilmer Eye Institute and two from Hôpital Pitié-Salpêtrière were specifically scrutinized for their potential to overrepresent certain findings. To address these overlaps, we contacted the corresponding authors to confirm that the cohorts were assembled by different research teams. Additionally, we cross-checked details of each case to ensure no individual case was included more than once in our analysis.

Data extraction: Two authors (X.Z. and B.C.) independently extracted data from the selected studies into a pre-defined Excel spreadsheet template, and data were cross-verified by a third researcher (S.S.). The extracted data included general study information (authors, year of publication), study design (prospective or retrospective), participant characteristics (age, sex, diagnosis criteria), details of anterior visual pathway involvement, treatments administered, outcomes measured (visual acuity, relapse rates, MRI findings), and follow-up periods.

We used the term ‘incidence’ to describe the proportion of patients exhibiting specific clinical manifestations related to neurosarcoidosis within the total cohort analyzed. Given the frequent bilateral presentation of NSAVP, we quantified visual outcomes and associated clinical features on a per-eye basis. This approach was used for measurements including visual field defect, ptosis, proptosis, disc swelling, disc atrophy, normal disc appearance, disc hemorrhage, retinal hemorrhage, uveitis, vasculitis, and chorioretinitis. Demographic and disease-specific characteristics such as age, sex, and disease duration were calculated on a per-person basis.

The involvement of the anterior visual pathway across studies was categorized into three groups.: 1. Optic neuritis, if specified in the literature; 2. granuloma, if the cohort presented with at least one case of optic disc granuloma; and 3. other anterior visual pathway manifestations/ optic neuropathies. Changes in visual acuity, whether improvement or deterioration, were recorded directly from the articles if reported. If not explicitly stated, they were determined by comparing the lowest recorded vision (nadir) with the vision at the final follow-up. Vision was considered stable if the final follow-up measurement matched the vision at nadir or if stability was directly reported in the soure article. Progressive visual loss was classified when any of the following applied: (1) the source explicitly used the term "progressive" to describe pre-treatment vision decline; (2) the source reported deterioration from baseline prior to treatment even without exact acuity values; or (3) exact acuity data showed a reduction of ≥2 Snellen lines (or a logMAR increase ≥0.2) between baseline and nadir before treatment initiation. For those studies that reported the duration of visual loss or time to nadir vision before the initiation of treatments, we divided the disease course into acute (<48 h), subacute (48 h to 6 weeks) and chronic (> 6 weeks).

To assess visual outcomes, patients were categorized into two treatment groups: those who received only steroids and those who received both steroids and immunosuppressants. This classification allowed for a comparative analysis of treatment effectiveness between the groups.

A relapse was defined based on two criteria: either 1) direct reporting of a relapse in the source articles, or 2) inferred from clinical reports of deteriorating visual acuity or other systemic worsening that led to a change in treatment for a duration exceeding one month. Relapses were categorized based on treatment received at the time of recurrence: 'relapse on steroid' if occurring during steroid treatment alone, or 'relapse on immunosuppressant' if occurring on combined steroid and immunosuppressant therapy. We abstracted per-patient counts of ≥2 relapses. Studies that mentioned multiple relapses without exact counts were excluded from pooling. Series labelled "stable at last visit" contributed to relapse analyses only if median follow-up ≥12 months (or explicit relapse surveillance).

For this analysis, only the first relapse in each eye, along with the medications in use at the time, was recorded. No subsequent relapses were included in the calculation of the pooled 'incidence of relapse'. Cases lacking specific follow-up durations or reporting deceased participants were reported as 'no follow-up time'.

In instances where data were ambiguous or missing, the corresponding authors of the studies were contacted via email for clarification or additional information. Studies for which required data remained incomplete or unobtainable after three months without a response were excluded from the outcome-specific analysis. Throughout the selection and extraction processes, any disagreements between the researchers were resolved through discussion. If a consensus could not be achieved, a senior researcher (T.A.) was consulted to make the final decision.

2.5. Statistics

Statistical analyses were performed using R (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria). The Freeman–Tukey variant of the arcsine square transformation was used for proportional data, with a fixed-effects model applied in cases of low heterogeneity ($p > 0.1$, $I^2 < 50$ %). Significant heterogeneity ($p < 0.1$, $I^2 > 50$ %) prompted sensitivity and subgroup analyses to explore sources of variance. Random-effects models were used if heterogeneity remained unresolved, and clinical homogeneity was assessed as present. Publication bias was evaluated using funnel plots and the Egger's test, with statistical significance set at $p < 0.05$.

3. Result

3.1. Study characteristics

Overall, we initially identified 2567 potentially relevant studies. After removing duplicates and screening titles and abstracts, we reviewed the full texts of 127 articles. Ultimately, 33 studies involving 334 patients (404 eyes) met the inclusion criteria for our meta-analysis. All articles were retrospective case series, with the largest study including 52 patients. The screening process was presented in the PRISMA flowchart (Fig. 1), and the main characteristics of the selected studies are summarized in Supplementary Table 1.

3.2. Demographic characteristics

As shown in Table 1, across 33 studies comprising 334 adults, neurosarcoidosis with AVP involvement presented predominantly at ages 18–39 years (pooled incidence 56 %, 95 % CI [47 %–66 %]), followed by 40–59 years (pooled incidence 37 %, 95 % CI [27 %–46 %]). Females comprised 69 % (95 % CI [59 %–78 %]). By ethnicity, prevalence was highest among African patients (pooled incidence 45 %, 95 % CI [24 %–67 %]), followed by Caucasian (pooled incidence 32 %, 95 % CI [16 %–49 %]) and Asian (pooled incidence 11 %, 95 % CI [2 %–23 %]). As summarized in Supplementary Table 2, the studies were conducted between 1972 and 2022. All were retrospective case series: two multicentre cohorts, four two-centre cohorts, and the remainder were single-centre cohorts. Geographically, there were 21 studies from the United States, four from the United Kingdom, two from India, two from France, one from Japan, and one from Norway. Median follow-up ranged from 0.3 to 8 years. Approximately 18 % (95 % CI [9 %–29 %]) of cases had a CNS biopsy, and 53 % (95 % CI [48 %–64 %]) had biopsy evidence outside the CNS.

3.3. Clinical manifestations

The primary symptoms of AVP involvement in neurosarcoidosis were visual loss and visual field defects, while ocular pain, diplopia, and proptosis were less frequent (Table 2). The pooled incidence of bilateral optic nerve involvement was 46 % (95 % CI [34 %–58 %], I2 = 65 %, $p < 0.01$, Table 2). Most patients did not exhibit systemic sarcoidosis symptoms before the onset of ophthalmic symptoms (pooled incidence 78 %, 95 % CI [65 %–88 %], I2 = 43 %, p = 0.03). Progressive visual loss was the most common presentation (pooled incidence 63 %, 95 % CI [47 %–78 %], I2 = 28 %, $p = 0.18$). The most frequently reported ophthalmological findings included relative afferent pupillary defect (RAPD), followed by uveitis, vasculitis, and chorioretinitis (Table 2). Optic disc swelling was the most common disc appearance, followed by disc atrophy, normal disc, and disc hemorrhages. In addition, 3th – 7th cranial nerves, lacrimal gland and/or orbital, and conjunctival were reported as sites of involvement concomitant with optic nerve involvement, with a fairly low pooled incidence of below 20 % for each. Seven cohorts reported time to nadir vision or duration of visual loss for at least three patients, the pooled incidence of acute visual loss was 3 % (95 % CI [1 %–13 %]; $I^2 = 0$ %, sub-acute visual loss was 35 % (95 % CI [20 %–51 %]; $I^2 = 0$ %, and chronic visual loss was 60 % (95 % CI [42 %–77 %]; $I^2 = 14$ %.

3.4. Diagnosis, laboratory tests and radiology

Among the 27 studies reporting the Neurosarcoidosis Consortium Consensus Group classification most cases were classified as probable or possible, The most common biopsy sites were endobronchial ultrasound (EBUS) and lung, while optic nerve, CNS, and orbital biopsies were less frequent (Table 3). Elevated white blood cell count (monocytes and/or lymphocytes, more than 5) in the cerebrospinal fluid (CSF, pooled incidence 51 %, 95 %CI[28 %–74 %], $I^2 = 69$ %, $p < 0.01$), elevated

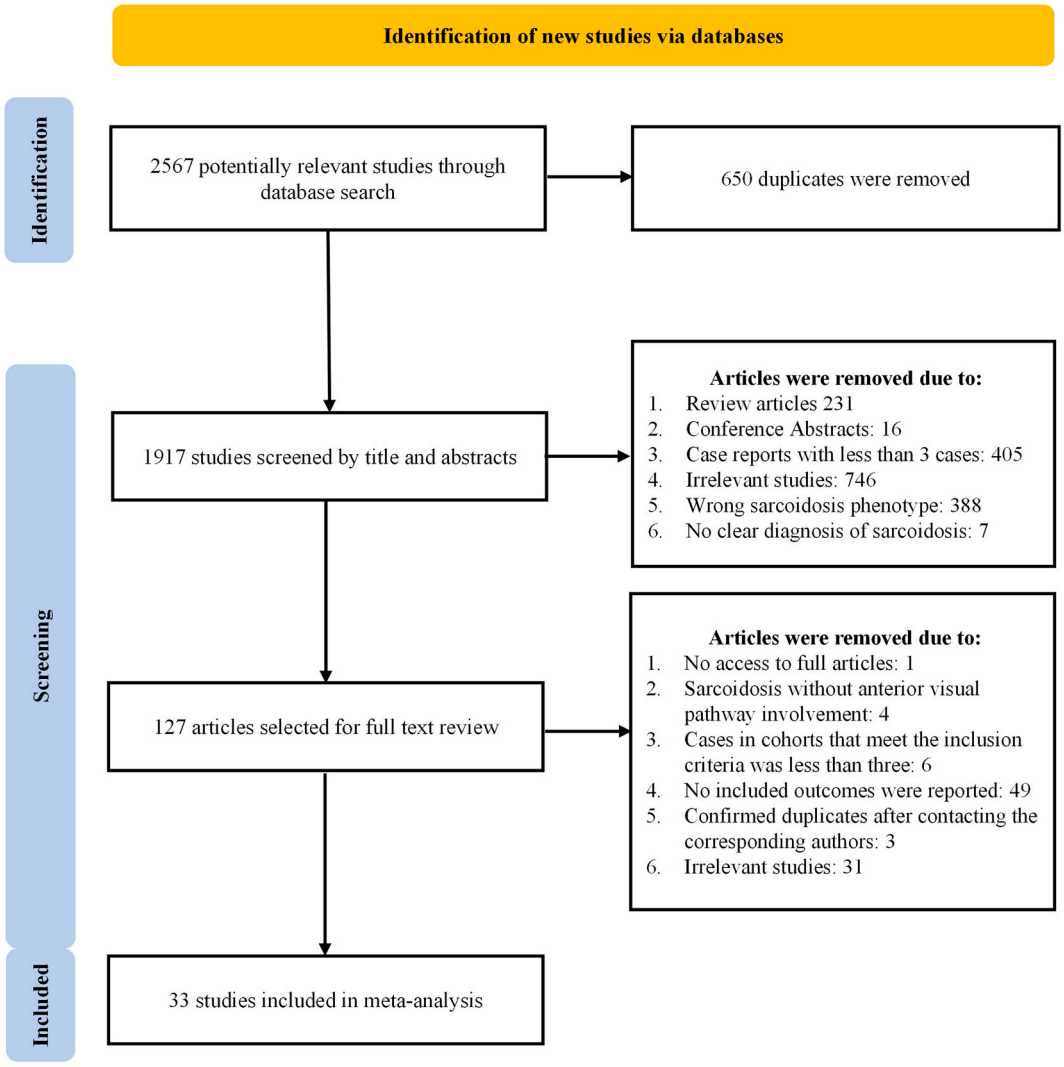

Fig. 1. PRISMA flowchart of data selection.

Table 1
Demographic characteristics and symptoms of neurosarcoidosis with AVP involvement.

Category	Study No.	Pooled incidence	95 %CI		P of Chi-square	I^2	Sensitivity analysis	Selected model
Races								
African	17	45 %	24 %	67 %	<0.01	75 %	Negative	Random
Asian	17	11 %	2 %	23 %	<0.01	63 %	Negative	Random
Caucasian	17	32 %	16 %	49 %	<0.01	69 %	Negative	Random
Hispanic	17	0 %	0 %	1 %	0.99	0 %	Negative	Fixed
Age								
18–39	25	56 %	47 %	66 %	0.13	24 %	Negative	Fixed
40–59	25	37 %	27 %	46 %	0.32	10 %	Negative	Fixed
≥ 60	25	1 %	0 %	6 %	1.00	0 %	Negative	Fixed
Gender								
Female	29	69 %	59 %	78 %	<0.01	44 %	Negative	Random

protein levels in CSF (as reported in the study, or over 60 mg/mL in studies without a reported reference range; pooled incidence 50 %, 95 % CI[32 %–68 %], $I^2 = 49$ %, $p < 0.01$), and elevated serum Angiotensin-converting enzyme (ACE) levels (higher than 40 nmol/mL/min, pooled incidence 43 %, 95 %CI[31 %–55 %], $I^2 = 45$ %, $p < 0.01$) were the most commonly reported laboratory abnormalities. The pooled incidence of hilar lymphadenopathy on CXR or CT was 51 % (95 %CI [40 %–61 %], $I^2 = 119$ %, $p = 0.24$).

The pooled incidence of anterior visual pathway involvement in MRIs in neurosarcoidosis subjects was is 63 % (95 %CI[43 %–81 %], $I^2 = 86$ %, $p < 0.01$) and optic nerve hyperintensity in 60 % (95 % CI: 38 %–80 %, $P < 0.01$). Cerebral white matter hyperintensity was observed in 26 % of cases (95 % CI: 8 %–47 %, $P < 0.01$), while sella, chiasm, or suprasellar region involvement was less frequent at 19 % (95 % CI: 8 %–33 %, $P < 0.01$). Lacrimal sac or orbital enhancement was rare, occurring in 10 % of cases (95 % CI: 4 %–17 %, $P = 0.21$).

Table 2
Clinical characteristics of neurosarcoidosis with AVP involvement.

Category	Study No.	Pooled incidence	95 %CI		P of Chi-square	I^2	Sensitivity analysis	Selected model
Side								
Bilateral (pooled)	29	46 %	34 %	58 %	<0.01	65 %	Negative	Random
Bilateral (optic neuritis)	3	15 %	0 %	47 %	0.57	0 %	Negative	Fixed
Symptoms								
Visual loss	22	94 %	86 %	99 %	0.01	45 %	Positive	Random
Visual Field Defect	21	79 %	72 %	85 %	0.35	8 %	Negative	Fixed
Ocular Pain	21	28 %	19 %	39 %	0.03	39 %	Negative	Random
No prior systemic sarcoidosis symptom	19	78 %	65 %	88 %	0.03	43 %	Positive	Random
No prior systemic sarcoidosis symptom (ON)	3	62 %	30 %	91 %	0.18	42 %	Negative	Fixed
Progressive vision loss	10	63 %	47 %	78 %	0.18	28 %	Positive	Fixed
Diplopia	23	8 %	1 %	17 %	0.03	39 %	Negative	Random
Ptosis	23	1 %	0 %	5 %	0.93	0 %	Negative	Fixed
Proptosis	23	8 %	3 %	16 %	0.62	0 %	Negative	Fixed
Ophthalmological Examination								
RAPD	15	73 %	63 %	83 %	0.41	4 %	Positive	Fixed
Disc swelling/granuloma	25	40 %	29 %	51 %	<0.01	64 %	Negative	Random
Disc atrophy	25	37 %	26 %	47 %	<0.01	59 %	Negative	Random
Normal disc	22	9 %	3 %	17 %	0.01	46 %	Negative	Random
Disc hemorrhage	22	1 %	0 %	5 %	0.24	16 %	Negative	Fixed
Retinal hemorrhage	13	1 %	0 %	8 %	0.33	11 %	Positive	Fixed
Uveitis (vitreous cells)	24	29 %	17 %	42 %	<0.01	73 %	Negative	Random
Anterior/intermediate Uveitis	8	49 %	14 %	85 %	<0.01	64 %	Negative	Random
Pan/post uveitis	8	51 %	15 %	86 %	<0.01	64 %	Negative	Random
Vasculitis/Vascular sheath	15	20 %	6 %	37 %	<0.01	72 %	Negative	Random
Chorioretinitis	21	16 %	6 %	28 %	<0.01	71 %	Negative	Random
Lacrimal gland/orbital involvement/conjunct	16	10 %	4 %	16 %	0.60	0 %	Negative	Fixed
Conjunctival involvement	15	4 %	0 %	13 %	0.02	46 %	Negative	Random
3rd – 7th cranial nerve involvement	12	17 %	8 %	31 %	0.03	49 %	Negative	Random

Table 3
Diagnostic characteristics of neurosarcoidosis.

Category	Study No.	Pooled incidence	95 %CI		P of Chi-square	I^2	Sensitivity analysis	Selected model
Zajicek Criteria								
Definite	27	18 %	9 %	29 %	<0.01	59 %	Negative	Random
Probable	27	53 %	41 %	64 %	<0.01	55 %	negative	Random
Possible	27	16 %	5 %	29 %	<0.01	77 %	negative	Random
Isolated	21	3 %	0 %	12 %	<0.01	53 %	Negative	Random
Biopsy								
Respiratory system	23	43 %	31 %	55 %	<0.01	42 %	Negative	Random
Lymph node	24	12 %	4 %	23 %	0.02	42 %	Negative	Random
Skin	24	0 %	0 %	2 %	0.87	0 %	Negative	Fixed
Optic Nerve	24	9 %	1 %	21 %	<0.01	60 %	Negative	Random
CNS	24	7 %	3 %	13 %	0.67	0 %	Negative	Fixed
Orbit /Lacrimal Sac/EOM	24	4 %	1 %	8 %	0.31	11 %	Negative	Fixed
Chest CT Typical Changes								
hilar lymphadenopathy (CXR or CT)	15	51 %	40 %	61 %	0.24	19 %	negative	Fixed
CSF								
Protein elevated(>60)	17	50 %	32 %	68 %	0.01	49 %	negative	Random
CSF ACE elevated (>2)	5	12 %	0 %	64 %	<0.01	75 %	negative	Random
Cells elevated (>5)	17	51 %	28 %	74 %	<0.01	69 %	negative	Random
Opening Pressure(>20)	8	20 %	0 %	51 %	0.08	44 %	negative	Fixed
OCB Positive	7	10 %	3 %	19 %	0.21	29 %	negative	Fixed
Serum ACE	23	43 %	31 %	55 %	0.01	45 %	negative	Random
MRI								
AVP overall involvement	20	63 %	43 %	81 %	<0.01	86 %	Negative	Random
ON hyperintensity/enhancement in T2 Signal	18	60 %	38 %	80 %	<0.01	86 %	Negative	Random
Enhancement/ Hyperintensity in white matter	8	26 %	8 %	47 %	<0.01	75 %	Negative	Random
Sella/chiasm/pituitary/suprasellar area involvement	23	19 %	8 %	33 %	<0.01	75 %	Negative	Random
Lacrimal sac/EOM/orbital fat enhancement	8	10 %	4 %	17 %	0.21	27 %	Positive	Fixed

3.5. Current treatments

As shown in Fig. 2, the pooled incidence of systemic steroid administration was 100 % (95 % CI [98 %–100 %], $I^2 = 0$ %, $p = 0.61$), with 82 % receiving high-dose steroids (> 40 mg/day) (95 % CI [59 %–98 %], $I^2 = 66$ %, $p < 0.01$) (Table 4). For secondary immunosuppressants and monoclonal antibodies, we included only studies published after the first reported use of such treatments- azathioprine in 1988 (Gelwan et al., 1988)) and infliximab in 1996 (Anthony et al., 2016) The pooled incidence of secondary immunosuppressive use was 44 % (95 % CI[28 %–59 %], $I^2 = 78$ %, $p = 0.01$). Since only nine studies reported the use of monoclonal antibodies in neurosarcoidosis with AVP involvement, it was difficult to determine the overall incidence precisely. The pooled incidence of patients receiving monoclonal antibodies due to optic nerve sarcoidosis across all studies was 3 % (95 % CI [0 %–7 %], $I^2 = 35$ %, $p = 0.07$).

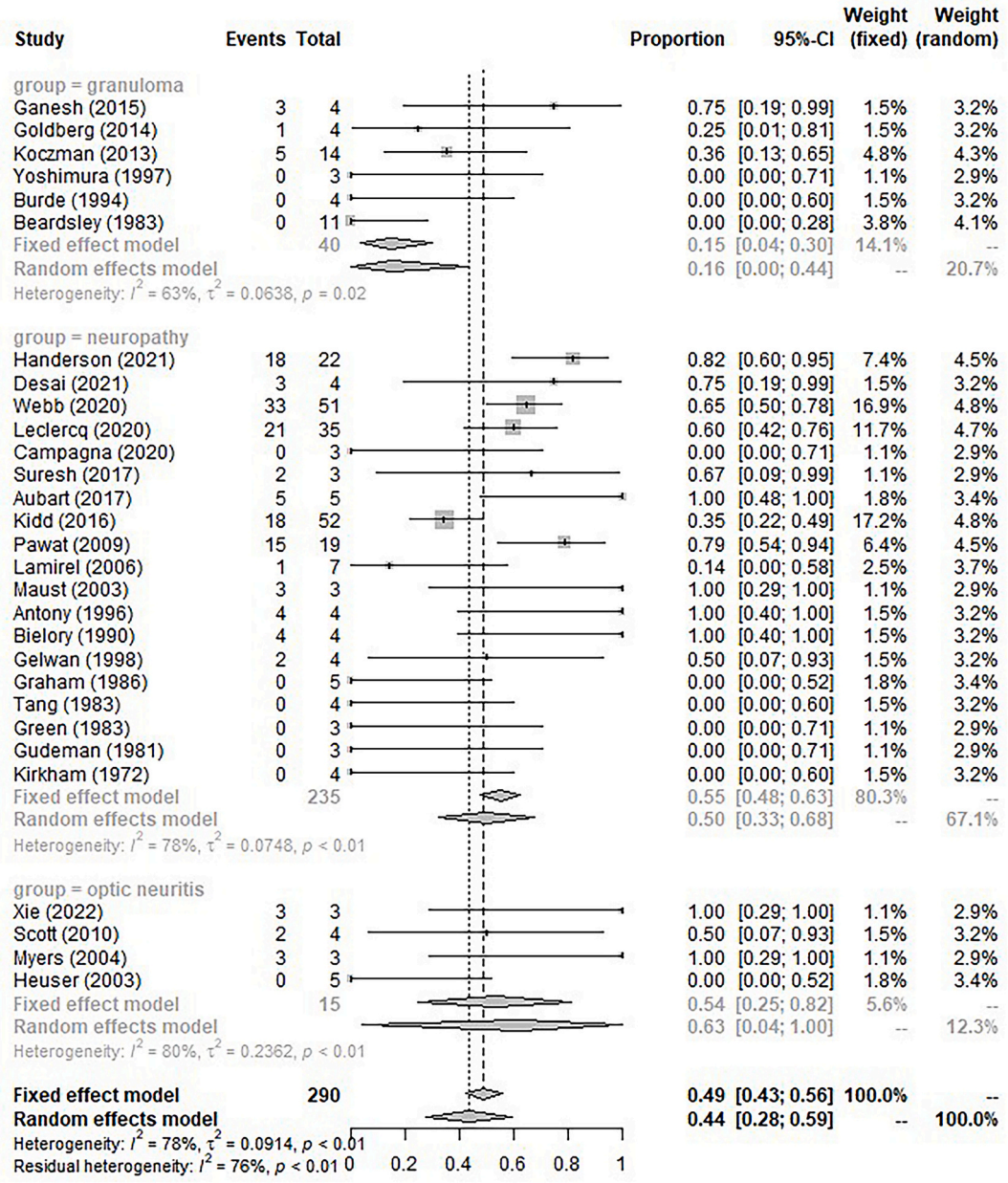

Fig. 2. Forest Plot of immunosuppressives utilization in NSAVP.

3.6. Visual outcomes

Baseline visual acuity, defined as the lowest reported vision before any treatment, had a pooled incidence of 53 % for vision equal to or worse than 20/80 (95 % CI [44 %–63 %], I^2 = 37 %, p = 0.03). The incidence of no light perception (NLP) was 6 % (95 % CI [1 %–12 %], I^2 = 39 %, p = 0.02). After treatment, 57 % of eyes showed visual improvement (95 % CI [50 %–63 %], I^2 = 27 %, p = 0.10), 24 % had stable vision (95 % CI [17 %–32 %], I^2 = 16 %, p = 0.25), and 20 % experienced worsened vision (95 % CI [14 %–26 %], I^2 = 29 %, p = 0.08). Overall, 72 % of eyes had a final vision better than 20/200 (95 % CI [65 %–78 %], I^2 = 21 %, p = 0.18), with 10 % with NLP vision (95 % CI [5 %–15 %], I^2 = 32 %, p = 0.07). The incidence of relapse was 34 % (95 % CI [24 %–44 %], I^2 = 29 %, p = 0.10). All are shown in Table 3. Of the 24 studies reporting relapse information, seven mentioned events after the first; two did not provide exact counts and were excluded. Eleven studies met criteria for the ≥2-relapse analysis (five with non-zero counts; six zero-event cohorts with median follow-up ≥12 months). The pooled incidence of patients with ≥2 relapses was 9 % (95 % CI [1 %–21 %]; I^2 = 8 %).

3.7. Visual outcomes by treatments

We compared visual outcomes between patients treated with steroids alone and those receiving both steroids and immunosuppressants (Table 4, Fig. 3). At baseline, 53 % (95 % CI [39 %–67 %], I^2 = 0 %, p = 0.83) of patients in the first group had visual acuity worse than 20/80, compared to 43 % (95 % CI [26 %–60 %], I^2 = 0 %, p = 0.48) in the second. Visual improvement was observed in 46 % (95 % CI [32 %–60 %], I^2 = 14 %, p = 0.31) of those receiving only steroids, while 44 % (95 % CI [27 %–61 %], I^2 = 44 %, p = 0.05) of patients who also received immunosuppressants showed improvement. Visual deterioration occurred in 12 % (95 % CI [3 %–23 %], I^2 = 0 %, p = 0.60) and 10 % (95 % CI [1 %–24 %], I^2 = 0 %, p = 0.56), respectively. A final vision better than 20/200 was achieved by 62 % (95 % CI [48 %–75 %], I^2 = 0 %, p = 0.55) in the steroid-only group and 70 % (95 % CI [55 %–83 %], I^2 = 0

Table 4
Pooled result of current therapies and treatment efficacy of optic neurosarcoidosis.

Category	Study No.	Pooled incidence	95 %CI		P of Chi-square	I^2	Sensitivity analysis	Selected model
Baseline Visual Acuity								
Better than 20/80	25	45 %	39 %	52 %	0.05	34 %	Negative	Fixed
Equals or worse than 20/80	25	53 %	44 %	63 %	0.03	37 %	Negative	Random
NLP	25	6 %	1 %	12 %	0.02	39 %	Negative	Random
Treatment								
Overall Steroid	31	100 %	98 %	100 %	0.61	0 %	Negative	Fixed
Overall High dose steroid	17	82 %	59 %	98 %	<0.01	66 %	Negative	Random
IV Steroid	17	31 %	22 %	40 %	0.13	29 %	Negative	Fixed
Immunosuppressives(after 1988)	29	44 %	28 %	59 %	<0.01	76 %	Negative	Random
AZA	16	11 %	5 %	18 %	0.17	25 %	Negative	Fixed
MTX	16	29 %	11 %	25 %	<0.01	71 %	Negative	Random
MMF	16	11 %	0 %	29 %	<0.01	79 %	Negative	Random
Monoclonal antibodies (after 1996)	19	3 %	0 %	7 %	0.07	35 %	Positive	Fixed
Visual Outcome								
Improved	27	57 %	50 %	63 %	0.10	27 %	Negative	Fixed
Stable	27	24 %	17 %	32 %	0.25	16 %	Negative	Fixed
Worse	27	20 %	14 %	26 %	0.08	29 %	Negative	Fixed
>20/200	24	72 %	65 %	78 %	0.18	21 %	Positive	Fixed
≤20/200	24	29 %	23 %	36 %	0.11	27 %	Positive	Fixed
NLP	24	10 %	5 %	15 %	0.07	32 %	Negative	Fixed
Incidence of relapse	24	34 %	24 %	44 %	0.10	29 %	Negative	Fixed

%, $p = 0.46$) among those receiving combination therapy. No light perception (NLP) was observed in 16 % (95 % CI [5 %–28 %], $I^2 = 0$ %, p = 0.46) of cases where only steroids were used, which decreased to 1 % (95 % CI [1 %–8 %], $I^2 = 40$ %, $p = 0.08$) in the presence of immunosuppressants. The incidence of relapse was also lower with the combined approach at 16 % (95 % CI [2 %–37 %], $I^2 = 29$ %, $p = 0.17$), compared to 40 % (95 % CI [25 %–55 %], $I^2 = 15$ %, p = 0.28) when steroids were used alone.

3.8. Subgroup study

We identified six cohorts with cases of optic disc granuloma and four cohorts with optic neuritis or perineuritis (Supplementary Table 1). Subgroup analysis of clinical manifestations, treatments, and visual outcomes are presented in Table 5.

4. Discussion

This is the largest systematic review of treatment and visual outcomes in neurosarcoidosis with anterior visual pathway involvement, reporting on 334 individual cases across 33 articles. We utilized 33 articles reporting on the treatment and visual outcomes of neurosarcoidosis with anterior visual pathway involvement (NSAVP).

We show that NSAVP predominantly affects females aged 18–40 years, with very low prevalence among individuals over 60 years of age. This demographic pattern aligns with that of general neurosarcoidosis (Bradshaw et al., 2021) and ocular sarcoidosis. African individuals exhibit the highest incidence of NSAVP, followed by Caucasians. Although our search strategy did not exclude non-English studies, primarily using English-language databases may have introduced a selection bias affecting the apparent ethnic distribution of NSAVP.

Our findings reveal that systemic steroids are universally used as the primary treatment, with a significant proportion of patients also receiving steroid-sparing immunosuppressants such as methotrexate, azathioprine, and mycophenolate mofetil (pooled incidence 44 %, 95 % CI [28 %59 %]). Monoclonal antibodies like infliximab and adalimumab are less frequently used (pooled incidence 3 %, 95 % CI [0 %–10 %).

4.1. Clinical manifestations and course

Overall, our meta-analysis reveals that bilateral involvement is highly prevalent, occurring in 46 % of all AVP- involving neurosarcoidosis cases but only 15 % of cases of optic neuritis. More than half of the patients had progressive visual loss, a relative afferent pupillary defect (RAPD), visual field defects, an absence of prior sarcoid symptoms. Notably, the pooled incidence of ocular pain was 28 % (CI [19 %–39 %]), substantially less than the 86 % associated with myelin oligodendrocyte glycoprotein-related disease (MOGRD) (Chen et al., 2018) and 90 % in multiple sclerosis (MS) (Bennett et al., 2023). This is consistent with previous reports (Kidd et al., 2016), which suggest that NSAVP tends to follow a less painful, more progressive course than demyelinating optic neuritis. Because most source studies did not report exact time-to-nadir vision, we were limited to summarizing the proportion of patients whose vision deteriorated within a predefined window, which may mask important differences in presentation tempo and treatment timing. Future work should use larger, preferably prospective cohorts with standardized, granular reporting of exact time-to-nadir (in days) to enable finer subtyping (acute vs. subacute) and more robust prognostic and treatment-response analyses.

The appearance of the optic disc at the onset of NSAVP was heterogenous; the pooled incidences of disc swelling, atrophy, and normal disc appearance were 40 %, 37 %, and 9 %, respectively.

Intraocular inflammation, orbital and cranial nerve involvement by sarcoidosis were concomitant findings collectively represented in 56 % of cases, showing that while these are important in aiding the diagnosis of neurosarcoidosis, isolated anterior visual pathway disease occurs in nearly half of presentations. The incidence of intraocular inflammation was less than 30 %, but the prevalence of uveitis varied significantly across studies, from 73 % (Frohman et al., 2003) to a complete absence (Gelwan et al., 1988; Campagna et al., 2019; Graham et al., 1986; Maust et al., 2003). Cohorts that mentioned vitritis or cells in the vitreous were included as intermediate/posterior uveitis in this review (Standardization of Uveitis Nomenclature (SUN), 2021). Fewer than 10 % of patients presented with diplopia, ptosis, or proptosis and the involvement of 3rd to 7th cranial nerve was 17 %. We recognize that there were insufficient data to determine current uveitis disease activity and that we were unable to identify whether the presence of uveitis was accurately diagnosed/ excluded by non-uveitis specialists. Similarly, cranial nerve involvement may have been under-reported before MRI was routinely utilized (Billerot et al., 2023).

4.2. Diagnosis

Our classification of neurosarcoidosis cases primarily followed the

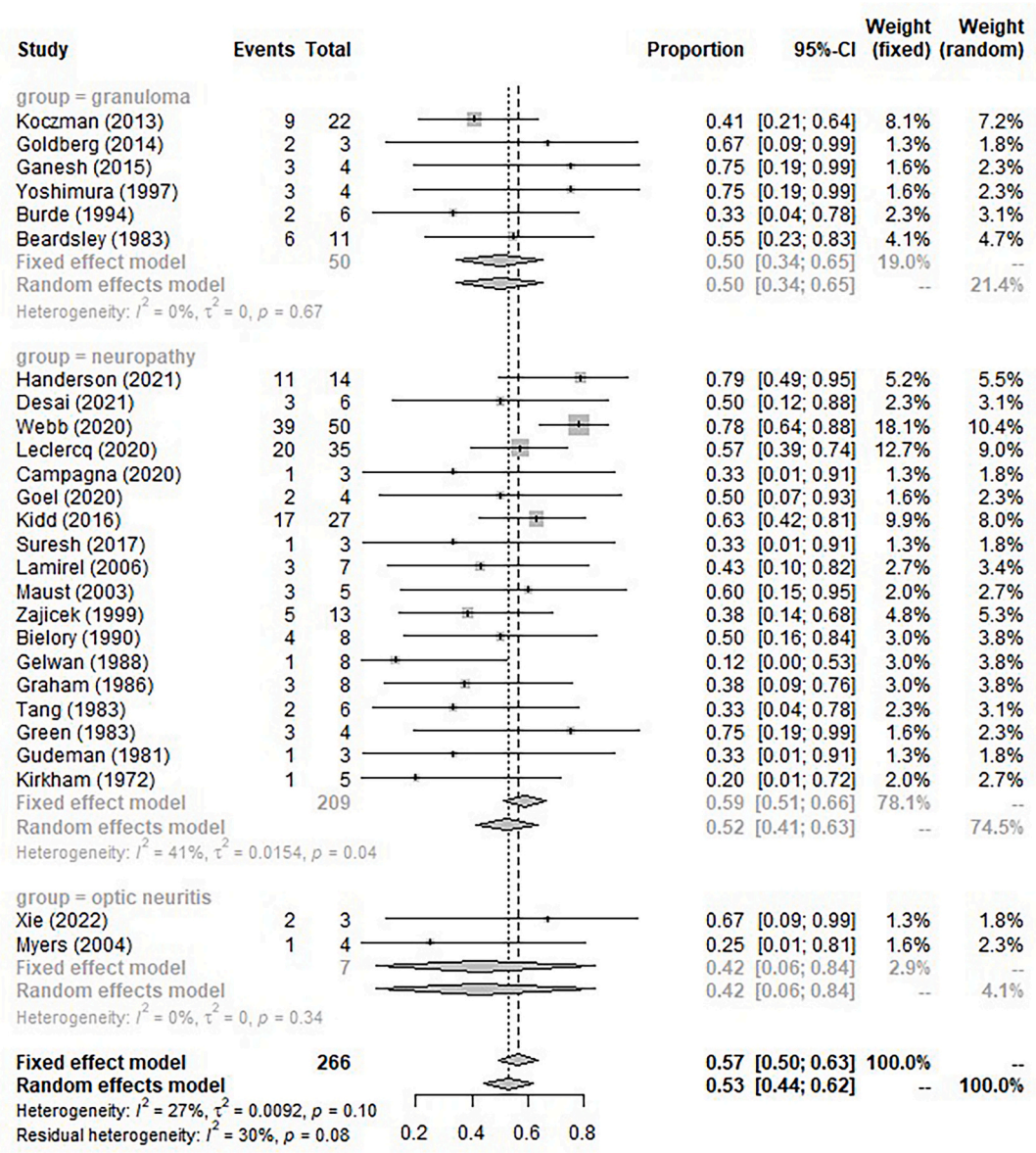

Fig. 3. Forest Plot of overall increase rate of visual acuity in NSAVP.

guidelines established by Zajicek et al. (Zajicek et al., 1999) and the Neurosarcoidosis Consortium Consensus Group's 2018 diagnostic criteria (Stern et al., 2018). In 16 % of cases, a tissue diagnosis was not available, and biopsy-confirmed evidence was lacking. Two cohorts included only biopsy-proven cases without differentiating between 'definite' and 'probable' classifications. Additionally, four cohorts did not provide enough information to fit into any of the above diagnostic categories, though they represented a small subset with minimal impact on our overall findings.

Our analysis shows that the detection of hilar lymphadenopathy via chest X-ray (CXR) or computed tomography (CT) scans, alongside elevated cell counts and protein concentrations in CSF, were each positive in over 50 % of cases. This was followed by serum ACE levels, corroborating diagnostic trends observed in the neurosarcoidosis literature (Arun et al., 2020; Barreras and Stern, 2022). In the two cohorts that reported Positron Emission Tomography–Computed Tomography (PET-CT) of the chest findings, 73 % (Henderson et al., 2021) and 79 % (Webb et al., 2021) of patients had positive PET-CT results, highlighting the potential value of this imaging modality in diagnosing neurosarcoidosis cases.

4.3. Treatment trends and visual outcomes by treatment group

Our research highlights the widespread use of steroids as the primary treatment for NSAVP. Recent studies show a growing preference for traditional immunosuppressives, including azathioprine (AZA, pooled incidence 11 %), methotrexate (MTX, 29 %), and mycophenolate mofetil (MMF, 11 %). These treatments were used in over 50 % of cases. Since 1996, only 3 % of patients received monoclonal antibody therapies, with infliximab being the most frequently reported (7 cohorts), followed by adalimumab and rituximab (2 cohorts each). One cohort referenced a TNF-alpha analogue without specifying the type (Kidd, 2018).

At presentation, most patients had significantly reduced vision, with 53 % experiencing 20/80 or worse, regardless of whether one or both eyes were affected. Following treatment, 57 % showed significant visual improvement, while 25 % experienced stabilization. However, despite combined treatment, 30 % of patients still had a visual prognosis worse than 20/200, which emphasizes the need to explore third-line treatments. Visual outcomes were relatively consistent across studies, in contrast to the variability seen in disease manifestations.

While rates of visual improvement, stabilization, and decline did not

Table 5
Pooled result of visual outcomes from different therapies.

Category	Study No.	Pooled incidence	95 %CI	P of Chi-square	I^2	Sensitivity analysis		Selected model
Steroid								
Baseline VA > 20/80	14	41 %	27 %	55 %	0.92	0 %	Negative	Fixed
Baseline VA ≤20/80	14	53 %	39 %	67 %	0.83	0 %	Negative	Fixed
Improve	14	46 %	32 %	060 %	0.31	14 %	Negative	Fixed
Stable	14	34 %	21 %	48 %	0.61	0 %	Negative	Fixed
Decrease	14	12 %	3 %	23 %	0.60	0 %	Negative	Fixed
>20/200	14	62 %	48 %	75 %	0.55	0 %	Negative	Fixed
≤20/200	14	38 %	25 %	52 %	0.55	0 %	Negative	Fixed
NLP	15	16 %	5 %	28 %	0.46	0 %	Negative	Fixed
Incidence of relapse	16	40 %	25 %	55 %	0.28	15 %	Negative	Fixed
Steroid and Immunosuppressant								
Baseline VA > 20/80	10	44 %	27 %	61 %	0.30	16 %	Negative	Fixed
Baseline VA ≤20/80	10	43 %	26 %	60 %	0.65	0 %	Negative	Fixed
Improve	11	44 %	27 %	61 %	0.05	44 %	Negative	Fixed
Stable	11	37 %	12 %	63 %	<0.01	57 %	Positive	Random
Decrease	11	10 %	1 %	24 %	0.56	0 %	Negative	Fixed
>20/200	11	70 %	55 %	83 %	0.46	0 %	Negative	Fixed
≤20/200	11	30 %	17 %	45 %	0.46	0 %	Negative	Fixed
NLP	11	1 %	1 %	8 %	0.08	40 %	Negative	Fixed
Incidence of relapse	11	16 %	2 %	37 %	0.17	29 %	Negative	Fixed

significantly differ between treatment groups, combined therapy was linked to a lower incidence of NLP (1 %, 95 % CI [1 %–8 %] vs. 16 %, 95 % CI [5 %–28 %]) and a reduced relapse rate (16 %, 95 % CI [2 %–37 %] vs. 40 %, 95 % CI [25 %–55 %]).

A comparative cohort study on general neurosarcoidosis found MTX more effective than MMF in reducing relapse rates, though only two patients had cranial nerve involvement (Xie et al., 2021). Another study reported MMF as the least effective treatment (Desai et al., 2021). There is limited research on the use and effectiveness of monoclonal antibodies in NSAVP. While infliximab has shown promise in preventing relapses in general neurosarcoidosis (Fritz et al., 2020; Goldberg et al., 2016), evidence for adalimumab remains scarce. Despite combined therapy, the high incidence (30 %) of a poor visual prognosis underscores the need for alternative treatment strategies. We acknowledge that the short and inconsistent reporting in small case series presented a limitation in calculating prognostic data. Future large-scale cohort studies, even retrospective ones, could assess treatment efficacy more comprehensively.

Although our primary analysis counted only the first relapse per patient for comparability, the pooled estimate incorporating zero-event cohorts with adequate follow-up indicates a subset (9 %) who experiences multiple relapses (≥2), consistent with a treatment-refractory disease course in some individuals. These findings should be interpreted cautiously given the small number of contributing studies and heterogeneous follow-up. Future studies should systematically characterize the clinical phenotype and evaluate treatment responses in patients with multiple relapses to better inform therapeutic strategies.

The manifestations of NSAVP most frequently reported are heterogeneous; they include optic neuritis (Xie et al., 2021), compressive or infiltrative optic neuropathy (Desai et al., 2021), increased intracranial pressure, chronic uveitis (Goldberg et al., 2016), retinal or choroidal ischemia or glaucoma (Kidd et al., 2016). Understanding outcomes based on specific NSAVP presentations requires subgroup analysis which was challenging as the majority of cohorts were mixed. We identified four articles focusing exclusively on optic neuritis secondary to neurosarcoidosis; five outcomes (bilateral involvement, systemic manifestations, AVP involvement, steroid administration, and monoclonal antibody administration) could be quantitatively synthesized (Supplementary Table 3). We observed less bilateral involvement (15 %), more cases where prior symptoms of systemic sarcoidosis were absent, and more AVP abnormalities on MRI compared with mixed cohorts. Optic neuritis was not frequently painful (28 %). Since optic neuritis is the chief cause of visual loss, these observations highlight the importance of reporting on optic neuritis cohorts in neurosarcoidosis to better phenotype and understand this presentation. Future studies with larger and more focused cohorts are needed to address this gap.

There are limitations to this study. First, the evidence base is entirely retrospective, and the included studies span five decades (1972–2022), during which diagnostic criteria, imaging availability, and treatment practices evolved, introducing potential misclassification and era effects.The lack of multicenter, comparative studies limits the strength of evidence for the efficacy of treatments for NSAVP. Additionally, follow-up time varied widely across the studies, which may have influenced results. Lastly, because most source studies did not report exact time-to-nadir vision, we were limited to summarizing the proportion of patients whose vision deteriorated within a predefined window, which may mask important differences in presentation tempo and treatment timing. Future work should use larger, preferably prospective cohorts with standardized, granular reporting of exact time-to-nadir (in days) to enable finer subtyping (acute vs. subacute) and more robust prognostic and treatment-response analyses.

This is the first meta-analysis to evaluate the clinical manifestations, treatment and visual outcomes of neurosarcoidosis with anterior visual pathway involvement and represents the largest study population to date (334 individuals). Our analysis provides novel insights into the natural history of neurosarcoidosis with anterior visual pathway involvement and indicates that combining steroids with immunosuppressants leads to better visual outcomes although larger and more contemporary cohorts are needed. Future research should focus on specific NSAVP manifestations and their treatment responses to refine management strategies.

CRediT authorship contribution statement

Xia Zhang: Writing – original draft, Data curation, Conceptualization. **Xinyu Zhao:** Methodology, Formal analysis. **Bo Chen:** Writing – review & editing, Data curation. **Lukasz Lagojda:** Methodology, Data curation. **Eva Oustabassidis:** Data curation. **Tarunya Arun:** Writing – review & editing, Data curation, Conceptualization. **Srilakshmi Sharma:** Writing – review & editing, Data curation, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors affirm that no generative AI or AI-assisted technologies were used in the writing, editing, or data analysis of this manuscript.

Declaration of competing interest

Dr. Tarunya Arun has received honoraria, speaker fees, research grants, or consulting fees for participation in advisory boards, steering committees, and data and safety monitoring committees from Janssen, Merck, Novartis, Roche, and Sanofi. These activities are unrelated to the present study. All other authors declare no competing interests.

All other authors declare no conflicts of interest relevant to the content of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jneuroim.2025.578761.

Data availability

The data supporting the findings of this meta-analysis were extracted from previously published studies, which are cited within the manuscript. All data generated or analyzed during this study are available in the article and its supplementary materials. Further details are available from the corresponding author upon reasonable request.

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Glossary

CNS: central nervous system
NSAVP: Neurosarcoidosis with anterior visual pathway involvement
AVP: Anterior visual pathway
CSF: Cerebrospinal fluid
ACE: Angiotensin-Converting Enzyme
NLP: no light perception
WASOG: World Association of Sarcoidosis and Other Granulomatous Disorders
RAPD: relative afferent pupillary defect
EBUS: endobronchial ultrasound
CXR: Chest X-ray
CT: Computed Tomography
CI: Confidence Interval
PET-CT: Positron Emission Tomography–Computed Tomography
MOGRD: Myelin Oligodendrocyte Glycoprotein-Related Disease
AZA: Azathioprine
MTX: Methotrexate
MMF: Mycophenolate Mofetil