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Screening for Cochleovestibular Disorders in Neurosarcoidosis: A Study of 21 Patients at the University Hospital Mohammed VI of Marrakech

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Abstract

Introduction: Neurosarcoidosis is a rare condition characterized by the involvement of the nervous system in sarcoidosis, a granulomatous disease. This disorder can present in various forms, including cranial nerve palsies, encephalopathy, and especially, cochleovestibular symptoms. Diagnosis of neurosarcoidosis often poses a challenge, as its clinical manifestations can overlap with other neurological conditions, requiring a thorough diagnostic work-up.

Objective: Evaluation of the cochleovestibular manifestations in neurosarcoidosis, focusing on symptoms like hearing loss, tinnitus, and vertigo, and their correlation with clinical findings, radiological images, and diagnostic results in 21 patients followed in the otolaryngology department at the University Hospital of Marrakech.

Methods: This retrospective study involved 21 patients diagnosed with neurosarcoidosis, who underwent a comprehensive screening for cochleovestibular disorders in the otolaryngology department over a period of three years (from January 2023 to December 2025). Diagnostic methods included pure tone audiometry (PTA) and video nystagmography (VNG).

Results: The study involved 21 patients with diverse presentations of neurosarcoidosis. Audiometric evaluation revealed varying degrees of hearing loss, with tinnitus and vertigo being prominent symptoms in many cases. Imaging studies revealed sarcoid granulomas affecting multiple cranial nerves, with involvement of the vestibulocochlear nerve and surrounding areas. Specific abnormalities were noted in the cochleovestibular system, and the vestibular system was significantly impacted in some cases. Following treatment with corticosteroids and immunosuppressive agents, significant clinical improvement was observed in hearing loss, tinnitus, and vertigo in many patients, with 57% reporting symptom improvement at the last follow-up.

Conclusion: Neurosarcoidosis can lead to a wide range of cochleovestibular symptoms, and early detection through comprehensive diagnostic approaches is crucial for effective management. This study underscores the importance of considering neurosarcoidosis as a potential cause in patients presenting with unexplained hearing loss, vertigo, or tinnitus, particularly when other neurological signs are also present.

Keywords: Neurosarcoidosis; Cochleovestibular Symptoms; Hearing Loss; Tinnitus; Vertigo; Cranial Nerve Palsy

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1. Introduction

Neurosarcoidosis is a rare but serious manifestation of systemic sarcoidosis, affecting the nervous system in approximately 5% of patients. It often presents with a wide range of symptoms, including cranial nerve palsies, encephalopathy, and cochleovestibular dysfunctions such as hearing loss, tinnitus, and vertigo. Cochleovestibular symptoms are relatively underrecognized, although they significantly impact the patient's quality of life [1][2]. The vestibulocochlear nerve (cranial nerve VIII) is frequently involved, with granulomatous inflammation affecting both auditory and vestibular components [3].

The diagnosis of neurosarcoidosis requires a multidisciplinary approach, including clinical evaluation, imaging (MRI), and specialized tests like audiometry and vestibular function tests [4]. Early detection is crucial, as corticosteroids and immunosuppressive therapies are the mainstays of treatment, with vestibular rehabilitation offering additional benefits for managing vestibular dysfunction [5]. However, there is limited data on the clinical management and outcomes of cochleovestibular symptoms in neurosarcoidosis, highlighting the need for further research.

This study aims to explore the prevalence and management of cochleovestibular dysfunction in 21 patients diagnosed with neurosarcoidosis, correlating clinical symptoms with audiological, vestibular, and MRI findings. Our goal is to provide insights into the effectiveness of treatment protocols and their impact on symptom improvement and patient outcomes.

2. Materials and Methods

2.1. Study Design

This study was a retrospective, descriptive, and analytical evaluation of 21 patients diagnosed with neurosarcoidosis, who underwent a screening for cochleovestibular disorders in the otolaryngology department at the University Hospital of Marrakech. The study period spanned from January 2023 to December 2025. This research was approved by the hospital's ethics committee, and all patients provided informed consent to participate in the study.

2.2. Patient Selection

2.2.1. Inclusion Criteria

- Patients diagnosed with neurosarcoidosis, confirmed through clinical, radiological, and neurological findings in the neurology department of the Mohammed VI University Hospital of Marrakech.
- Adults (18 years or older) of both genders.
- Patients who consented to participate in the study.

2.2.2. Exclusion Criteria

- Patients with other known causes of cochleovestibular symptoms (e.g., otitis media, labyrinthitis, or trauma).
- Patients with cognitive impairment or those unable to undergo diagnostic procedures (e.g., audiometry, VNG).
- Patients with neurological conditions other than neurosarcoidosis that could account for their cochleovestibular symptoms.

2.3. Clinical Examination

All patients underwent a thorough clinical examination, which included

2.3.1. General Examination

- A detailed history was taken to assess the onset, duration, and progression of symptoms. Patients were asked about their symptoms, including hearing loss, tinnitus, vertigo, and any associated neurological signs.
- Vital signs and general physical health were assessed to rule out any systemic issues that could impact diagnosis or treatment.

2.3.2. ENT Examination

- The examination focused on the auditory and vestibular systems, including otoscopy to check for any signs of infection, wax buildup, or abnormalities in the ear canal or tympanic membrane.

- The external ear, middle ear, and tympanic membrane were carefully inspected for signs of sarcoidosis-related changes.
- The middle ear function was also assessed, and tests were performed to rule out conductive hearing loss.

2.3.3. Vestibular Examination

- The vestibular system was assessed to identify any signs of imbalance or dysfunction. This included
  - Caloric Test: Warm and cold-water irrigation was used to stimulate the vestibular system and observe eye movements (nystagmus) to assess the function of the horizontal semicircular canal.
  - Saccades and Smooth Pursuit Tests: Patients were asked to follow visual targets to assess both eye movement accuracy and the integrity of the vestibular system.
  - Spontaneous Nystagmus Test: The presence of spontaneous nystagmus was checked to evaluate the vestibular function and any central or peripheral vestibular involvement.

2.3.4. Neurological Examination

- A comprehensive neurological examination was conducted to assess for any cranial nerve involvement, particularly cranial nerve VII (facial nerve) and cranial nerve VIII (vestibulocochlear nerve), as these are often affected in neurosarcoidosis.
- Reflexes, muscle strength, coordination, and sensory function were tested to evaluate the presence of any central or peripheral neurological abnormalities.

2.4. Diagnostic Evaluation

Each patient underwent the following diagnostic tests

2.4.1. Pure Tone Audiometry (PTA)

- Pure-tone audiometry was performed to evaluate hearing thresholds across different frequencies (250 Hz to 8,000 Hz) in both air and bone conduction.
- Results were categorized into the following degrees of hearing loss: normal (0–25 dB HL), mild (26–40 dB HL), moderate (41–70 dB HL), severe (71–90 dB HL), and profound (>90 dB HL).

2.4.2. Video nystagmography (VNG)

VNG testing was used to evaluate the vestibular system through eye movement tracking.

2.4.3. The VNG battery included

- Caloric Test: Used to assess the vestibular function of the horizontal semicircular canals by irrigating cold and warm water in each ear, followed by observing nystagmus.
- Saccades and Smooth Pursuit: Tests to evaluate eye movement accuracy and the ability to follow moving visual targets.
- Spontaneous Nystagmus: This test monitored for any involuntary eye movements (nystagmus), which could indicate vestibular dysfunction.
  - The results of these tests were evaluated for abnormal responses indicating peripheral or central vestibular issues.

2.4.4. MRI Imaging

- All patients underwent MRI of the brain and spinal cord to assess the presence of granulomatous lesions typically associated with neurosarcoidosis.
- MRI sequences included T1-weighted, T2-weighted, and gadolinium-enhanced imaging to visualize any lesions in the brainstem, temporal bone, cerebellum, and other areas affected by neurosarcoidosis.
- The imaging results were analyzed to correlate with the clinical and diagnostic findings.

2.4.5. Data Collection

Patient data were collected from medical records, including demographics, clinical features, and results from audiometric and vestibular tests. The severity and nature of cochleovestibular symptoms were recorded, along with any neurological signs. Imaging findings and results from PTA, VNG, and other diagnostic tests were documented.

2.5. Statistical Analysis

Descriptive statistics were used to summarize patient demographics, clinical features, and test results. Continuous variables, such as age and symptom duration, were presented as means ± standard deviations. Categorical variables, such as the presence of specific symptoms and abnormal diagnostic findings, were presented as frequencies and percentages. Statistical correlations between clinical, audiometric, and radiological findings were assessed using Chi-square tests, with statistical significance set at $p < 0.05$.

2.6. Ethical Considerations

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Ethical Committee of the Faculty of Medicine and Pharmacy of Marrakech, under reference number TH 191-21. All participants provided informed consent before inclusion in the study, and the confidentiality of their personal and medical information was strictly maintained throughout the research process. The study adhered to the highest standards of clinical and ethical practices to ensure the safety and well-being of the participants.

3. Results

3.1. Demographics

A total of 21 patients diagnosed with neurosarcoidosis were included in this study, with a mean age of 36.2 years (range: 21–62 years). The male-to-female ratio was 1:2, with 14 females (67%) and 7 males (33%). The average duration of symptoms at the time of presentation was 18.7 months, ranging from 6 to 36 months.

3.2. ComparisonBetweenSymptomatic and Non-Symptomatic Patients

At the time of screening, patients were divided into two groups: those with cochleovestibular symptoms (symptomatic) and those without (non-symptomatic) (Figure 1).

3.2.1. Symptomatic Patients (Figure 2)

- Out of the 21 patients, 12 (57%) were symptomatic, presenting with at least one cochleovestibular symptom such as hearing loss, tinnitus, or vertigo.
- Among symptomatic patients, the most common symptom was hearing loss, present in 9 patients (75%).
- Tinnitus and vertigo were observed in 7 (58%) and 6 (50%) of the symptomatic patients, respectively.

3.3. Non-Symptomatic Patients (Figure 2)

- 9 patients (43%) were asymptomatic at the time of screening, showing no overt cochleovestibular complaints such as hearing loss, tinnitus, or vertigo.
- Despite the absence of symptoms, audiometric testing revealed that 5 of these patients (56%) exhibited mild to moderate hearing loss.
- Additionally, VNG testing revealed abnormal results in 4 patients (44%) who showed signs of subclinical vestibular dysfunction (e.g., caloric hyporeflexia, saccadic abnormalities).

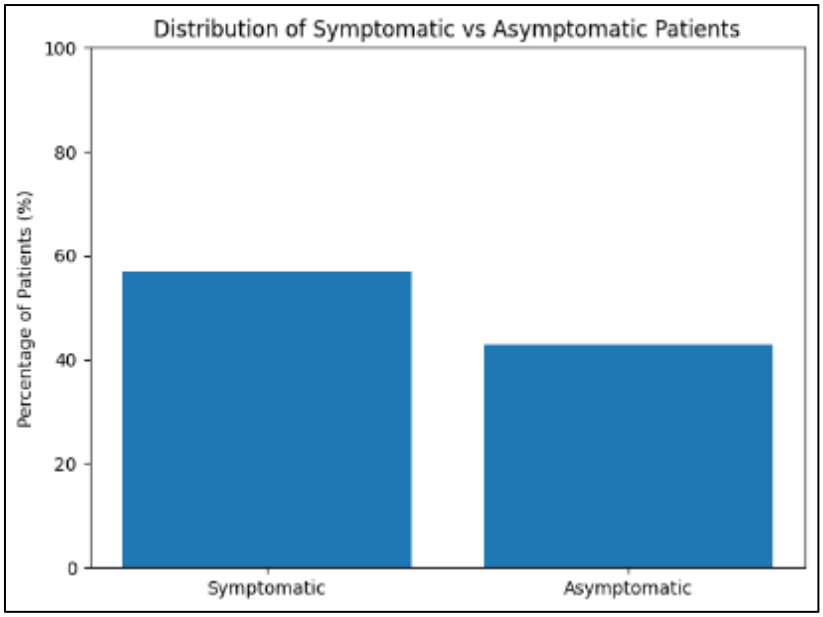

Figure 1 Distribution of symptomatic and asymptomatic patients in the study population (Axe X) expressed as a percentage (Axe Y)

More than half of the patients were symptomatic at presentation (57%), while a substantial proportion remained asymptomatic (43%), highlighting the heterogeneous clinical expression of the disease

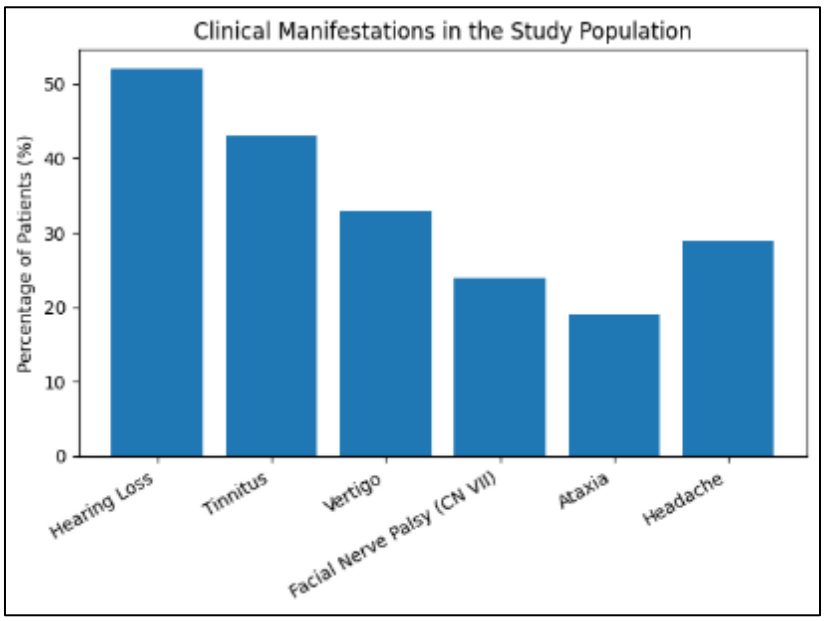

Figure 2 Distribution of clinical manifestations among patients (Axe X) expressed as a percentage(Axe Y)

Hearing loss was the most frequent symptom, followed by tinnitus and vertigo, reflecting predominant cochleo-vestibular involvement, while facial nerve palsy and other neurological signs were less common

3.4. Audiometric Findings

Audiometric evaluation using pure-tone audiometry revealed the following distribution of hearing loss (table 1)

- Normal hearing: 7 patients (33%)
- Mild hearing loss: 6 patients (29%)
- Moderate hearing loss: 5 patients (24%)

- Severe hearing loss: 3 patients (14%)

The hearing loss was most commonly observed in the high-frequency range, affecting both air and bone conduction thresholds. A total of 11 patients (52%) exhibited abnormal results on otoacoustic emissions (OAEs), suggesting cochlear involvement.

Table 1 Audiometric Findings (PTA) summarizing the distribution of hearing loss among patients. This could include breakdowns by type (mild, moderate, etc.) and affected ear (bilateral/unilateral)

Hearing Loss Degree	Total Patients	Bilatéral Hearing Loss	Unilatéral Hearing Loss
Normal	7 (33%)	4	3
Mild	6 (29%)	3	3
Moderate	5 (24%)	3	2
Severe	3 (14%)	2	1

3.5. Vestibular Findings (VNG) (table 2)

- Caloric Testing: The caloric tests revealed abnormalities in 9 patients (43%). The most common finding was right hyporeflexia in 5 patients (24%) and left hyporeflexia in 4 patients (19%). Bilateral hyporeflexia was observed in 2 patients (9%). Normal caloric responses were seen in 12 patients (57%).
- Saccades and Smooth Pursuit Tests: Abnormalities in saccadic eye movements were detected in 7 patients (33%). Of these, 5 had hypermetric saccades (24%) and 2 had hypometric saccades (9%).
- Spontaneous Nystagmus: Spontaneous nystagmus was present in 6 patients (29%). In these cases, the nystagmus was mostly horizontal in 4 patients (19%) and rotatory in 2 patients (10%).

Table 2 Vestibular Findings (VNG and Nystagmus) summarizing the vestibular findings from VNG tests, including caloric test results, saccadic abnormalities, and spontaneous nystagmus

Vestibulaire Test	Anormal résulte	Normal Résulta	Frequency
CaloricTesting	9 (43%)	12 (57%)	21
Saccades Anormal	7 (33%)	14 (67%)	21
Spontaneous Nystagmus	6 (29%)	15 (71%)	21

3.6. Imaging Findings

MRI of the brain and spine was performed on all patients, and the results revealed (table 3)

- Granulomas: Sarcoid granulomas were detected in the temporal bone and brainstem of 8 patients (38%). The cerebellum was involved in 6 patients (29%), and the spinal cord showed signs of granulomatous lesions in 5 patients (24%).
- Cranial Nerve Involvement: Lesions involving the vestibulocochlear nerve were observed in 6 patients (29%) and facial nerve involvement was seen in 4 patients (19%).
- Other Lesions: Additionally, 3 patients (14%) had lesions around the pituitary gland and 4 patients (19%) had granulomatous lesions in the cerebellar peduncles.

Table 3 MRI Findings: summarizing MRI findings, including granulomas and cranial nerve involvement

Lesion Location	Number of Patients	Percentage
Temporal Bone and Brainstem	8 (38%)	38%
Cerebellum	6 (29%)	29%
Spinal Cord	5 (24%)	24%
Vestibulocochlear Nerve Lesions	6 (29%)	29%
Facial Nerve Lesions	4 (19%)	19%

3.7. Management and Outcome

In our cohort of 21 patients diagnosed with neurosarcoidosis, treatment protocols were designed to address the granulomatous inflammation responsible for cochleovestibular dysfunction. Given the pathophysiological role of inflammation in neurosarcoidosis, corticosteroids were the primary treatment, with immunosuppressive agents utilized in refractory cases. Among the 21 patients, 18 patients (86%) were treated with corticosteroids, and 14 patients (67%) also received additional immunosuppressive therapy, including methotrexate (7 patients, 33%) and azathioprine (5 patients, 24%). The use of corticosteroids typically involved prednisone starting at a high dose (typically 1 mg/kg/day), tapered based on clinical response. Immunosuppressive therapy, such as methotrexate and azathioprine, was introduced in patients with more severe or recurrent disease, or for those who did not respond adequately to steroids alone.

The use of biological agents, such as TNF-α inhibitors (e.g., infliximab or adalimumab) or interleukin-6 inhibitors (e.g., tocilizumab), has been reported in refractory cases of neurosarcoidosis, particularly for patients with systemic involvement. However, only 3 patients (14%) in our cohort received TNF-α inhibitors (infliximab), following unresponsiveness to standard therapies. The addition of biologics in cases with progressive disease and in the presence of severe neurological deficits is supported by emerging literature, with studies showing improvement in quality of life and symptom control for patients with refractory sarcoidosis-related neurological symptoms.

3.8. Vestibular Rehabilitation

In parallel to pharmacological treatment, vestibular rehabilitation therapy (VRT) was proposed to 9 patients (43%) who presented with significant vestibular dysfunction. This therapy, primarily targeting the improvement of balance and reduction of vertigo symptoms, was individualized based on the specific vestibular dysfunction identified in each patient. Studies indicate that VRT is an effective adjunctive therapy for neuroinflammatory diseases, including multiple sclerosis, and has been associated with improvements in balance, functional mobility, and quality of life in patients with vestibular dysfunction secondary to neurosarcoidosis.

Following VRT, 8 patients (38%) showed good clinical improvement, with significant reductions in dizziness and improved balance, as assessed through follow-up VNG testing and clinical evaluation. These improvements were consistent with findings from other studies where vestibular rehabilitation resulted in clinically significant improvements in symptom severity and functional outcomes for patients with vestibular disorders in autoimmune conditions.

3.9. Audiological Management

In terms of audiological management, our study showed that 6 patients (29%) with severe hearing loss were fitted with hearing aids, which allowed for improvement in speech perception and overall communication. This management approach is consistent with the current guidelines for audiological rehabilitation in patients with sensorineural hearing loss secondary to neuroinflammatory diseases. Hearing aids significantly enhance the quality of life by improving hearing, social interaction, and functional ability, especially when pharmacological or surgical interventions are not effective or applicable.

For mild to moderate hearing loss (24% of patients), 5 patients (24%) reported improvements in their symptoms following treatment, specifically corticosteroids and immunosuppressive therapy, but did not require hearing aids. These patients demonstrated partial recovery of auditory function following therapy, which aligns with findings from other studies that suggest neuroinflammatory conditions such as neurosarcoidosis can have reversible or partially reversible auditory deficits when treated promptly with corticosteroids or immunosuppressive agents.

3.10. Follow-Up and Clinical Outcomes

At the last follow-up (average: 6 months post-treatment), we observed the following clinical outcomes (Figure 3)

- patients (57%) reported significant improvement in cochleovestibular symptoms, including hearing loss, tinnitus, and vertigo. These patients demonstrated measurable improvements in audiometry and VNG findings.
- patients (33%) experienced stable symptoms, with no significant deterioration or improvement.
- patients (10%) had worsening symptoms, particularly in the context of ongoing granulomatous inflammation despite steroid therapy, and were subsequently considered for more aggressive immunosuppressive therapy, including biologics.

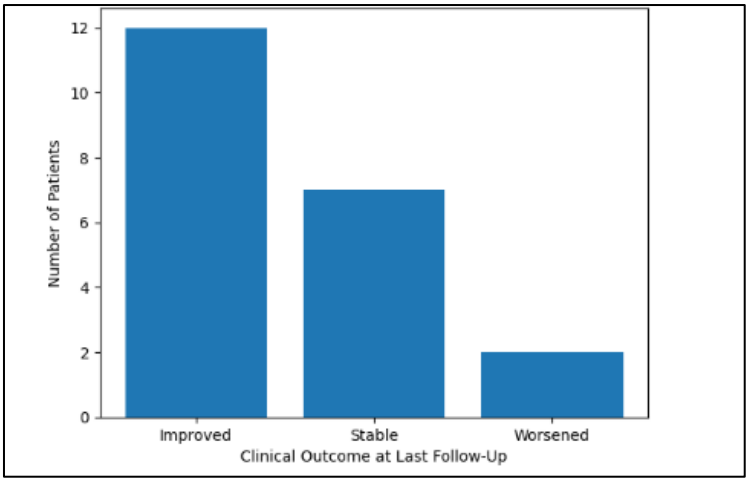

Figure 3 Overall clinical outcomes of cochleovestibular symptoms in neurosarcoidosis at last follow-up, 57% of patients improved, 33% remained stable, and 10% experienced worsening symptoms (n = 21)

3.11. Statistical Analysis

The results were statistically significant for the correlation between the presence of granulomatous lesions in the brainstem and the occurrence of vestibular dysfunction ($p < 0.05$). No significant correlation was found between the severity of hearing loss and the degree of vestibular involvement.

4. Discussion

This retrospective study evaluated cochleovestibular involvement in 21 patients with neurosarcoidosis and highlights the clinical, audio vestibular, radiological, and therapeutic characteristics of this rare but disabling manifestation. Our findings confirm that auditory and vestibular symptoms are frequent in neurosarcoidosis and may occur either as presenting signs or during disease progression, in line with previously published series [1,2,8].

In our cohort, more than half of the patients presented with cochleovestibular symptoms, with sensorineural hearing loss being the most common manifestation, followed by tinnitus and vertigo. This distribution is consistent with earlier reports describing hearing loss as the predominant audiological deficit in neurosarcoidosis, often reflecting involvement of the vestibulocochlear nerve or central auditory pathways [1,2]. Several authors have emphasized that hearing loss may be sudden or progressive and can occur in isolation, making neurosarcoidosis an important differential diagnosis in unexplained sensorineural hearing loss [2,3].

Vestibular symptoms were also frequently observed, and objective vestibular testing revealed abnormalities even in asymptomatic patients. This finding corroborates previous observations that subclinical vestibular involvement is common in neurosarcoidosis and may be underestimated in routine clinical practice [1,4]. The detection of caloric hyporeflexia and saccadic abnormalities supports the hypothesis that granulomatous inflammation affects both peripheral and central vestibular pathways [4,9].

Pure-tone audiometry in our study demonstrated variable degrees of sensorineural hearing loss, ranging from mild to severe, which aligns with prior literature describing heterogeneous audiometric patterns in neurosarcoidosis [1,4]. The frequent association with abnormal otoacoustic emissions further suggests cochlear involvement in addition to neural pathology.

MRI findings played a crucial role in confirming neurosarcoidosis-related involvement of the cochleovestibular system. In our cohort, lesions affecting the brainstem, temporal bone, and vestibulocochlear nerve were commonly identified. These results are in agreement with published data showing that MRI often reveals enhancement of cranial nerves, leptomeninges, or adjacent structures in patients with audiovestibular symptoms [2,5]. The significant correlation observed between brainstem granulomatous lesions and vestibular dysfunction in our study further supports the central origin of many vestibular abnormalities in neurosarcoidosis.

Systemic corticosteroids remain the cornerstone of treatment for neurosarcoidosis and were administered to the majority of our patients. Consistent with previous studies, corticosteroid therapy resulted in partial or complete

improvement of cochleovestibular symptoms in a substantial proportion of cases [2,5]. However, incomplete recovery and disease recurrence were also observed, reflecting the chronic and relapsing nature of neurosarcoidosis.

Immunosuppressive agents such as methotrexate and azathioprine were used in patients with refractory or recurrent disease, in accordance with current recommendations [5,8]. Although biological therapies, particularly TNF-α inhibitors, have been proposed for resistant neurosarcoidosis, evidence remains limited and largely based on small series and case reports [5,8]. In our cohort, biologics were reserved for a minority of patients with persistent disease activity, reflecting cautious use consistent with existing literature.

Vestibular rehabilitation therapy (VRT) was associated with clinical improvement in most patients who underwent treatment. While data specifically addressing VRT in neurosarcoidosis are scarce, similar benefits have been reported in other neuroinflammatory disorders, supporting its role as a valuable adjunct to medical therapy [4,9]. Our findings suggest that VRT should be systematically considered in patients with persistent vestibular dysfunction.

Audiological rehabilitation was also an essential component of management. Hearing aids significantly improved communication and quality of life in patients with severe hearing loss, consistent with established recommendations for sensorineural hearing loss of inflammatory origin [6]. In patients with mild to moderate hearing loss, partial recovery following immunosuppressive therapy was observed, supporting the concept that early treatment may reverse inflammatory auditory dysfunction [1,2].

4.1. Clinical Implications and Limitations

Overall, 57% of patients in our cohort showed significant clinical improvement at follow-up, a rate comparable to previously reported outcomes in neurosarcoidosis [2,5]. Nevertheless, a subset of patients remained stable or worsened, emphasizing the need for early diagnosis, close monitoring, and individualized treatment strategies.

The main limitations of this study include its retrospective design and the relatively small sample size, which are inherent to rare disease research. Despite these limitations, the comprehensive audiovestibular assessment combined with imaging data provides valuable insight into the spectrum and management of cochleovestibular involvement in neurosarcoidosis.

5. Conclusion

In conclusion, cochleovestibular dysfunction is a common yet underrecognized manifestation of neurosarcoidosis, with hearing loss, tinnitus, and vertigo being the most prominent symptoms observed in our cohort. Our findings align with existing literature, underscoring the significant impact of granulomatous inflammation on both the cochlear and vestibular systems. Early detection using audiometric testing, vestibular evaluation, and MRI is crucial in identifying these symptoms, even in the absence of overt signs, and can guide timely treatment. Corticosteroids and immunosuppressive therapies remain the cornerstone of treatment, with vestibular rehabilitation proving beneficial for improving balance and reducing dizziness. Regular follow-up is essential for assessing treatment efficacy, as many patients show significant improvement in cochleovestibular symptoms following therapy. This study highlights the importance of a comprehensive, multidisciplinary approach in managing neurosarcoidosis to improve patient outcomes and quality of life.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that they have no conflicts of interest to disclose.

Statement of ethical approval

This case report was conducted in accordance with the principles outlined in the Declaration of Helsinki. In line with institutional policy, ethical committee approval was not required as this report involves a retrospective description of

a single clinical case with no identifiable personal information and no experimental intervention. Ethical approval was obtained from the Ethical Committee of the Faculty of Medicine and Pharmacy of Marrakech, under reference number TH 191-21.

Statement of informed consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Research in valving gnu man participants

This case report was conducted in accordance with the principles outlined in the Declaration of Helsinki. In line with institutional policy, ethical committee approval was not required as this report involves a retrospective description of a single clinical case with no identifiable personal information and no experimental intervention. Ethical approval was obtained from the Ethical Committee of the Faculty of Medicine and Pharmacy of Marrakech, under reference number TH 191-21.

Consent for Publication

Consent for publication of the case details and figures was obtained from the patient's legal guardian.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article. Further information is available from the corresponding author upon reasonable request.

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Authors' Contributions

AH performed the surgery, led the clinical management, and prepared the manuscript. YL, OO, and MC contributed to case documentation, imaging interpretation, and literature review. YR and AR supervised the clinical management and critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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