SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2025; 42 (1): 15690 DOI: 10.36141/svdld.v42i1.15690

Cranial MRI in neurosarcoidosis: Imaging patterns and nationwide clinical correlations

Elif Uzun Ata[1], Serdar Can Guven[2], Orhan Kucuksahin[3], Mustafa Mahir Ulgu[4], Suayip Birinci[5]

[1]Ankara Bilkent City Hospital, Clinic of Radiology, Ankara, Turkey; [2]Ankara Bilkent City Hospital, Clinic of Rheumatology, Ankara, Turkey; [3]Ankara Yıldırım Beyazıt University Medical School, Department of Internal Medicine, Division of Rheumatology, Ankara, Turkey; [4]Ministry of Health, General Directorate of Health Information Systems, Ankara, Turkey; [5]Ministry of Health, Deputy Minister, Ankara, Turkey

Abstract. *Object:* To investigate cranial MRIs of sarcoidosis patients by defining typical and atypical findings and their relations with patient characteristics and other disease manifestations. *Materials and Methods:* A nationwide cohort was formed from patients with an entering ICD-10 code for sarcoidosis twice at least 1 month apart and any tissue biopsy result with the word "granuloma" defined in the biopsy report were considered to have sarcoidosis. Data regarding patients were obtained by using Turkish Ministry of Health National Electronic Data base. Patients of the formed cohort were investigated for the presence of a cranial imaging at any time. *Results:* 4367 patients were defined as sarcoidosis and enrolled in the study. 1659 cranial imagings in 689 patients were investigated. 1175 imagings were deemed suitable and evaluated. 3.4% of the patients had findings suggestive of sarcoidosis. Most common lesions were leptomeningeal or dural thickening with/without contrast material enhancement and midbrain/brainstem lesions. Presence of pulmonary sarcoidosis was the only significant factor with a negative predictive effect for patients to have typical findings. *Discussion:* Among sarcoidosis patients with MRI we detected 3.4% of them had findings suggestive of CNS sarcoidosis. Absence of pulmonary involvement was observed to be predictor for occurrence of typical manifestations.

Key words: sarcoidosis, cranial magnetic resonance imaging, neurosarcoidosis, mri findings, central nervous system sarcoidosis, big data in imaging, multicenter study

Introduction

Sarcoidosis is an immune-mediated disease characterized by non-caseating granuloma formations. Cardinal manifestation is pulmonary involvement with mediastinal lymph node enlargement and parenchymal changes in majority of patients, yet, as it is a notorious great mimicker, various other organ manifestations may occur during disease course. Sarcoidosis may affect both peripheral and central nervous system, being called "neurosarcoidosis". It had been reported that neurologic manifestations develop in 5-10% of sarcoidosis cases, yet various studies report different prevalence rates. Most common central nervous system (CNS) involvements of neurosarcoidosis comprise optic neuropathy, leptomeningitis, pachymeningitis, cranial mass lesions, encephalopathy, myelopathy, and hydrocephalus (1). Symptomatic CNS involvement has been reported to occur in approximately 5% of the cases, however autopsy studies revealed 15-25% of the cases had findings of CNS involvement. When CNS imaging findings were considered approximately 10% of the cases had changes compatible with CNS sarcoidosis (2-5). The most common imaging findings of intracranial sarcoidosis are meningitis characterized

Received: 1 February 2024
Accepted: 18 September 2024
Correspondence:
Serdar Can Güven
Ankara Bilkent Şehir Hastanesi, MH6 Onkoloji binası, Romatoloji bölümü, Bilkent, Çankaya, Ankara, Turkey, 06800
E-mail: drserdarguven@gmail.com
ORCID: 0000-0003-1965-9756

by leptomeningeal thickening and contrast enhancement particularly at the basis of the head, parenchymal granulomas, white-mater signal alterations, ventriculitis and hydrocephalus, spinal myelopathy, and cranial neuritis (2-9). Additionally, dura mater and cranial bones can be involved (8,9). Isolated CNS involvement can be seen less than 1% of sarcoidosis patients, however, in patients with multiple organ involvement, CNS symptoms generally surpass other accompanying manifestations when present (7). CNS sarcoidosis may result in serious morbidity and mortality therefore early recognition is crucial. Yet, as aforementioned, sarcoidosis can mimic various other medical conditions. This is also coherent in CNS imaging findings many of which can be observed in other conditions like infections, malignancies, and other autoimmune diseases. Especially in absence of other sarcoidosis manifestations and histopathologic proof of the disease, as CNS sampling could not always be available, diagnosing the disease can be quite a challenge. Therefore, radiologists should be aware of characteristic findings of CNS sarcoidosis to provide valuable information to clinicians for prompt diagnosis. Unfortunately, this may not be always the case since CNS findings of sarcoidosis is highly variable. Here in this nationwide, multicentre study, in a large cohort of sarcoidosis patients, we aimed to investigate imaging findings to further contribute to the current knowledge by defining typical and atypical findings and their relations with patient characteristics and other disease manifestations.

Methods

Study design

The study was designed as a retrospective, observational, nationwide, multi-centre study. Turkish Ministry of Health National Electronic Data base (e-Nabız) is used under supervision of Health Ministry to extract the data of the subjects. The e-Nabız system was established by the Health Ministry in 2015 as a national health information system, to which only authorized individuals and institutions have access, which has wide bandwidth and covers all of the country. E-Nabız system contains the clinical records of over eighty million people in Turkey including demographics, ever installed ICD codes, laboratory results, drug history, comorbidities. Ministry of Health presents services using Big Data technology, and these systems are also integrated together: E-Nabız and National Healthcare Information System (NHIS). With these integrated, systems data of the patients as of January1, 2016 up to date can be obtained.

Sarcoidosis diagnosis

A nationwide cohort was formed from patients with an entering ICD-10 code for sarcoidosis (D86.0, D86.1, D86.2, D86.3, D86.8, D86.9) twice at least 1 month apart between January 1, 2016 to December 31, 2022 and any tissue biopsy result with the word "granuloma" defined in the results section were considered to have sarcoidosis. Data regarding demographics, major involvements other than musculoskeletal involvements were recorded. Patients under the age of 18 and patients with a concomitant ICD code for tuberculosis at any time were excluded since differentiating two diseases retrospectively was quite not possible.

Radiologic evaluation

Patients of the formed cohort were investigated for the presence of a cranial imaging at any time. Results of these imaging's were evaluated by a radiologist for technical adequacy. Any imaging other than magnetic resonance imaging (MRI), technically inadequate imagings, imagings of the patients with history of cranial surgery and imagings with a missing result were all excluded. Typical findings were defined as leptomeningeal or dural thickening and/or contrast enhancement, nodular or mass lesions with continuity to dura mater and extra axial contrast enhancement, cranial nerve lesions, mid-brain and brainstem lesions, contrast-enhanced white-matter lesions, spinal signal alterations with contrast enhancement. Atypical lesions were defined as nonspecific T2 hyperintensities resembling microvascular angiopathy without contrast enhancement.

Statistical analyses

Statistical analyses were made by the Statistical Package for Social Sciences (SPSS) software version 20 (IBM Corp., Armonk, New York). Continuous variables were presented by mean ± standard derivation (SD) or median (min – max) according to normality and compared by student-T test or

Mann-Whitney-U test. Categorical variables were presented in numbers and percentages and compared by x^2 test. Binary logistic regression analysis was performed to investigate predictive factors for presence of typical imaging findings. p values < 0.05 were considered significant statistically.

Results

A total of 4367 patients were defined as sarcoidosis and enrolled in the study. 1659 cranial imagings in 689 patients were investigated. 1175 imagings were deemed suitable and evaluated. Among these 768 imagings were performed without intravenous contrast material and 407 with. In 584 imagings of 286 (6.5%) patients had MRI alterations. In 46 MRIs of 23 (0.5%) patients there were typical findings and in 263 (6.0%) patients had atypical findings. Among 667 patients whose MRIs were evaluated these frequencies are 39.3% and 3.4%, respectively. Typical findings in 46 MRIs are presented in Table 1.

Most common lesions were leptomeningeal or dural thickening with/without contrast material enhancement and midbrain/brainstem lesions. Figure 1 presents the constellation of typical findings in each MRI.

Clinical characteristics and sarcoidosis manifestations were compared in patients with an MRI result, between patients with normal MRI and patients with any finding (Table 2). Patients with MRI lesions were significantly older and female gender was more frequent. Average urinary calcium excretion was lower close to significance. When sarcoidosis manifestations were investigated, erythema nodosum (37 (12.9%) vs 33 (8.7%), p=0.075), hearing loss (34 (11.9%) vs 26 (6.8%), p=0.024), arrhythmia (15 (5.2%) vs 9 (2.4%), p=0.048) were more common and urolithiasis (16 (5.6%) vs 38 (10.0%), p=0.040) was less frequent in patients with a positive MRI. A similar analysis was performed between patients with typical MRI findings and patients with normal MRI (Table 2). Age did not differ between groups (52.50±24.75 vs 49.32±9.09, p=0.666). Level of median (IQR) urinary calcium excretion was lower in patients with typical findings (27.87 (81) vs 131.64 (222), p=0.035). Presence of pulmonary sarcoidosis was significantly lower in patients with typical findings (43.5% vs 66.9%, p = 0.023). Patients with typical findings were more frequently female (0.017) and had extra pulmonary manifestations more frequently such as facial paralysis, extra pulmonary lymphadenopathy, liver involvement, glomerulonephritis and myocarditis/pericarditis/cardiomyopathy (p values: 0.021, 0.018, <0.001, <0.001, <0.001, respectively).

Logistic regression analyses were performed to determinate predictive factors for patients to have both any positive MRI and an MRI with typical findings (Table 3). Age over 50 years (OR: 3.881, 95% [CI]: 2.759 – 5.641, p<0.001) and presence of hearing loss (OR: 1.924, 95% [CI]: 1.090 – 3.396, p=0.024) were positive predictive factors and presence of urolithiasis (OR: 0.486, 95% [CI]: 0.252 – 0.936, p=0.031) was a negative factor for patients to have a positive MRI. Presence of pulmonary sarcoidosis was the only significant factor with a negative predictive effect (OR: 0.325, 95% [CI]: 0.136 – 0.777, p=0.012) for patients to have typical MRI findings.

Table 1. Frequency of typical findings in MRIs

	N=46
Leptomeningeal or dural thickening with/without contrast enhancement, n (%)	33 (71.7)
Nodular or mass lesions with extra axial contrast enhancement, n (%)	14 (30.4)
Cranial nerve involvement, n (%)	9 (19.6)
White matter lesions with contrast enhancement, n (%)	25 (54.3)
Midbrain or brainstem lesions, n (%)	28 (60.9)
Spinal cord signal alterations with contrast enhancement, n (%)	5 (10.9)

Discussion

In our study we could evaluate 1175 MRI results of 667 patients in a cohort of sarcoidosis with 4367 patients. Out of these 667 patients, 381 had normal results, 286 had any lesions in 23 of which typical findings suggestive of sarcoidosis were detected. Most common lesions were leptomeningeal or dural thickening with/without contrast material enhancement and midbrain/brainstem lesions. When patients with a normal MRI and patients with any MRI findings were compared, older age and hearing loss were positive predictive factors and urolithiasis was a negative predictive factor for occurrence of lesions in MRI. When more typical lesions were taken into consideration, presence of pulmonary sarcoidosis was a negative predictive factor. Symptomatic

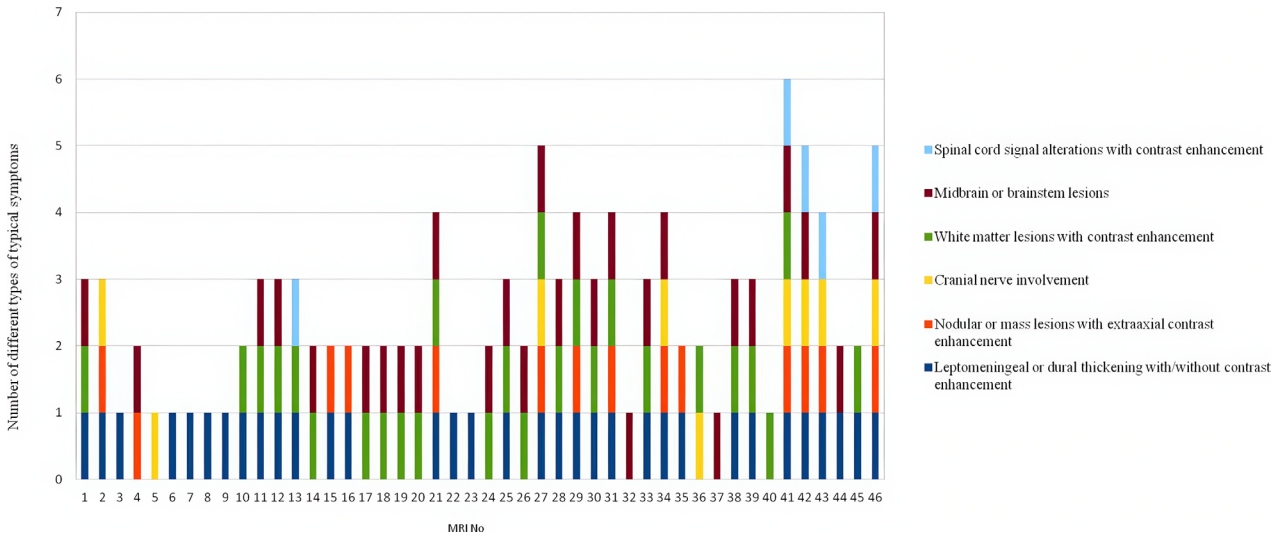

Figure 1. Constellation of typical findings in each MRI.

CNS involvement has been reported to occur in approximately 5% of the cases. This prevalence rises to 15-25% in postmortem studies and to approximately 10% in imaging studies (2-5). Our results demonstrated a frequency of 6.5% for presence of any MRI finding and 0.5% for findings more suggestive of CNS sarcoidosis. When only patients with an MRI considered these frequencies are 39.3% and 3.4%, respectively. However, the prevalence in our study should be interpreted with care since we could obtain imaging results as of 2016. Previous imagings could not be investigated. Sarcoidosis is a great mimicker. Involvements in organ systems may resemble various other conditions therefore exclusion and histopathologic confirmation is crucial. This is also the case in CNS involvement; however, tissue sampling may not be always possible and interpretation of cranial imaging, particularly MRI, comes forth for detecting CNS sarcoidosis. Additionally, 10-20% of neurosarcoidosis patients may not manifest any other organ involvement and recognition of imaging findings suggestive of sarcoidosis gains further importance (10-12). Unfortunately, CNS sarcoidosis does not have a pathognomonic finding. Yet, several studies defined cluster of some findings in varying frequencies, in sarcoidosis patients. Accordingly, most common CNS findings were reported to be cranial neuropathies (50-70%), leptomeningitis (10-20%), myelopathy (5-26%), parenchymal disease (up to 50%), hydrocephalus (10%) and hypothalamopituitary involvement (2-8%) (1, 2, 13-22). In our study among imaging findings, we accepted to be suggestive for sarcoidosis, the most common was leptomeningeal and/or dural involvement (71.4%). We could detect cranial nerve involvement only in 19.6% of the cases. None of our patients had hypothalamopituitary involvement, encephalitis, ventriculitis or hydrocephalus. Sarcoidosis patients may have isolated neurosarcoidosis approximately with a rate of 10-20% and less than 1% may have isolated CNS involvement. Since diagnosing CNS involvement is already a complicated process, defining some patient characteristics to predict occurrence of CNS involvement may be contributory to identification of these patients. In our study, among patients with MRI, we compared characteristics of patients which we could obtain through database, with normal MRI and with MRI alterations. Patients with MRI alterations were older and more frequently women. As for clinical characteristics, erythema nodosum, hearing loss and arrhythmias were more common. Interestingly, average urine calcium excretion was lower and history of urolithiasis was less frequent. When patients only with typical findings were evaluated, several etra pulmonary manifestations were more frequent and rate of pulmonary sarcoidosis was lower. Older age was not observed to be related with occurrence of typical findings. Regression analyses revealed age older than 50, hearing loss were positive predictors of MRI alterations while urolithiasis was a negative predictor. When regression analysis was performed to predict occurrence of MRI findings more suggestive of

Table 2. Characteristics of patients with MRI findings in comparison to patients with normal MRI

Number of patients with an evaluated MRI N=667					
	Patients with typical MRI findings N= 23	**Patients with typical and/or atypical MRI findings N= 286**	**Patients with normal MRI N=381**	**p***	**p****
Age, years, mean±SD	52.50±24.75	57.17±12.82	49.32±9.09	0.666	<0.001
Gender, female, n (%)	21 (91.3)	236 (82.5)	274 (71.9)	0.017	0.001
Average serum calcium levels, mg/dL, mean±SD	10.47±0.01	11.11±2.34	10.25±3.20	0.788	0.277
Average urinary calcium levels, mg/day, median (IQR)	27.87 (81)	87.10 (149)	131.64 (222)	0.035	0.098
Average serum ACE levels, mcg/L, median (IQR)	51.08 (59)	53.38 (46)	38.71 (49)	0.554	0.845
Average serum RF levels, U/ml, mean±SD	12.26±1.99	11.27±5.71	10.64±4.93	0.091	0.767
Patients with manifestations other than CNS, n (%)					
Pulmonary involvement (mediastinal lymphadenopathy and/or parenchymal disease)	10 (43.5)	190 (66.4)	255 (66.9)	0.023	0.893
Pulmonary hypertension	1 (4.3)	2 (0.7)	1 (0.3)	0.163	0.404
Uveitis	3 (13.0)	24 (8.4)	29 (7.4)	0.254	0.712
Erythema nodosum	3 (13.0)	37 (12.9)	33 (8.7)	0.583	0.075
Glandular involvement	11 (47.8)	139 (48.6)	201 (52.8)	0.425	0.288
Facial paralysis	2 (8.7)	9 (3.1)	10 (2.6)	0.021	0.688
Hearing loss	3 (13.0)	34 (11.9)	26 (6.8)	0.428	0.024
Lymphadenopathy	9 (39.1)	65 (22.7)	78 (20.5)	0.018	0.483
Liver involvement	1 (4.3)	1 (0.3)	0	<0.001	0.248
Glomerulonephritis	1 (4.3)	2 (0.7)	2 (0.5)	<0.001	0.773
Renal tubulopathy	1 (4.3)	6 (2.1)	4 (1.0)	0.263	0.270
Urolithiasis	1 (4.3)	16 (5.6)	38 (10.0)	0.511	0.040
Arrhythmia	1 (4.3)	15 (5.2)	9 (2.4)	0.901	0.048
Myocarditis/pericarditis/ cardiomyopathy	2 (8.7)	6 (2.1)	6 (1.6)	<0.001	0.615
Peripheral neuropathy	5 (21.7)	80 (28.0)	114 (29.9)	0.361	0.584
Mortality	1 (4.3)	11 (3.8)	18 (4.7)	0.843	0.582

*: p value between patients with typical MRI findings vs normal MRI, **: p value between patients with typical and/or atypical MRI findings vs normal MRI. *Abbreviations:* MRI: magnetic resonance imaging, ACE: angiotensin converting enzyme, RF: rheumatoid factor, CNS: central nervous system

sarcoidosis, only absence of pulmonary involvement was significantly related with presence of typical findings. Older age was not observed to be related with occurrence of typical findings. There are several limitations of our study. In addition to retrospective nature, data regarding patients were obtained from data base therefore, frequencies of disease manifestations should not be used for epidemiologic interpretations. Secondly, frequency of comorbidities which may affect particularly atypical lesions such as diabetes mellitus and hypertension were not evaluated. In addition, we could reach data as of 2016, previous examinations of patients could not be evaluated. Furthermore, as a nationwide, multicentre study, technicality of MRI procedure and reporting process was not unified. Finally, clinical impact

Table 3. Logistic regression analysis for predictive factors of any MRI findings and typical MRI findings

Predictive factors for any positive MRI findings			
Factor	**OR**	**95% [CI]**	**p**
Age > 50 years	3.881	2.759 – 5.641	<0.001
Hearing loss	1.924	1.090 – 3.396	0.024
Urolithiasis	0.486	0.252 – 0.936	0.031
Predictive factors for typical MRI findings			
Factor	**OR**	**95% [CI]**	**p**
Pulmonary involvement	0.325	0.136 – 0.777	0.012
Lymphadenopathy	2.232	0.905 – 5.507	0.081

of MRI findings could not be evaluated due to the methodology of the study. In conclusion, in this nationwide multicentre study comprising a large cohort of sarcoidosis patients, among patients with an MRI we detected 3.4% of them had findings suggestive of CNS sarcoidosis. Most common involvement was leptomeningitis and absence of pulmonary involvement was observed to be predictor for occurrence of typical manifestations. However, we wish to emphasize that due to nature of the study, these results can not represent true incidence of CNS lesions in sarcoidosis patients. Future prospective studies would contribute to the issue and defining of typical CNS involvements of sarcoidosis.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Bradshaw MJ, Pawate S, Koth LL, Cho TA, Gelfand JM. Neurosarcoidosis: Pathophysiology, Diagnosis, and Treatment. Neurol Neuroimmunol Neuroinflamm. 2021;4;8:e1084. doi: 10.1212/NXI.0000000000001084
2. Bathla G, Singh AK, Policeni B, Agarwal A, Case B. Imaging of neurosarcoidosis: common, uncommon, and rare. Clin Radiol. 2016;71:96–106. doi:10.1016/j.crad.2015.09.007
3. Hodge MH, Williams RL, Fukui MB. Neurosarcoidosis presenting as acute infarction on diffusion-weighted MR imaging: summary of radiologic findings. AJNR Am J Neuroradiol. 2007;28:84–86.
4. Brisman JL, Hinduja A, McKinney JS, Gerhardstein B. Successful emergent angioplasty of neurosarcoid vasculitis presenting with strokes. Surg Neurol. 2006;66:402–04. doi:10.1016/j.surneu.2006.02.048
5. Michotte A, Dequenne P, Jacobovitz D, Hildebrand J. Focal neurological deficit with sudden onset as the first manifestation of sarcoidosis: a case report with MRI follow-up. Eur Neurol. 1991;31:376–79. doi:10.1159/000116697
6. Macedo PJ, da Silveira VC, Ramos LT, et al. Isolated central nervous system vasculitis as a manifestation of neurosarcoidosis. J Stroke Cerebrovas Dis. 2016;25:e89–e92. doi: 10.1016/j.jstrokecerebrovasdis.2016.02.036.
7. Smith JK, Matheus MG, Castillo M. Imaging manifestations of neurosarcoidosis. AJR Am J Roentgenol. 2004;182:289 –95. doi: 10.2214/ajr.182.2.1820289
8. Pickuth D, Spielmann RP, Heywang-Kobrunner SH. Role of radiology in the diagnosis of neurosarcoidosis. Eur Radiol. 2000;10:941–944. doi: 10.1007/s003300051042
9. Zajicek JP, Scolding NJ, Foster O, et al. Central nervous system sarcoidosis: diagnosis and management. Q J Med. 1999;93:103–117. doi: 10.1093/qjmed/92.2.103
10. Scott TF, Yandora K, Valeri A, Chieffe C, Schramke C. Aggressive therapy for neurosarcoidosis: long-term follow-up of 48 treated patients. Arch Neurol. 2007;64(5):691-696. doi: 10.1001/archneur.64.5.691
11. Carlson ML, White JR Jr., Espahbodi M, et al. Cranial base manifestations of neurosarcoidosis: a review of 305 patients. Otol Neurotol. 2015;36(1):156-166. doi: 10.1097/MAO.0000000000000501
12. Gelfand JM, Bradshaw MJ, Stern BJ, et al. Infliximab for the treatment of CNS sarcoidosis: a multi-institutional series. Neurology. 2017;89(20):2092-2100. doi: 10.1212/WNL.0000000000004644
13. Krumholz A, Stern BJ. Neurologic manifestations of sarcoidosis. Handb Clin Neurol. 2014;119:305-333. doi: 10.1016/B978-0-7020-4086-3.00021-7
14. Pawate S, Moses H, Sriram S. Presentations and outcomes of neurosarcoidosis: a study of 54 cases. QJM. 2009;102(7):449-460. doi: 10.1093/qjmed/hcp042
15. Mekinian A, Maisonobe L, Boukari L, et al. Characteristics, outcome and treatments with cranial pachymeningitis: a multicenter French retrospective study of 60 patients. Medicine (Baltimore). 2018;97(30):e11413. doi: 10.1097/MD.0000000000011413
16. Koczman JJ, Rouleau J, Gaunt M, Kardon RH, Wall M, Lee AG. Neuro-ophthalmic sarcoidosis: the University of Iowa experience. Semin Ophthalmol. 2008;23(3):157-168. doi:10.1080/08820530802007382
17. Durel CA, Marignier R, Maucort-Boulch D, et al. Clinical features and prognostic factors of spinal cord sarcoidosis: a multicenter observational study of 20 BIOPSY-PROVEN patients. J Neurol. 2016;263(5):981-990. doi: 10.1007/s00415-016-8092-5
18. Soni N, Bathla G, Pillenahalli Maheshwarappa R. Imaging findings in spinal sarcoidosis: a report of 18 cases and review of the current literature. Neuroradiol J. 2019;32(1):17-28. doi: 10.1177/1971400918806634
19. Zalewski NL, Krecke KN, Weinshenker BG, et al. Central canal enhancement and the trident sign in spinal cord sarcoidosis. Neurology. 2016;87(7):743-744. doi: 10.1212/WNL.0000000000002992
20. Murphy OC, Salazar-Camelo A, Jimenez JA, et al. Clinical and MRI phenotypes of sarcoidosis-associated myelopathy. Neurol Neuroimmunol Neuroinflamm. 2020;7(4):e722. doi:10.1212/NXI.0000000000000722
21. Anthony J, Esper GJ, Ioachimescu A. Hypothalamic-pituitary sarcoidosis with vision loss and hypopituitarism: case series and literature review. Pituitary. 2016;19(1): 19-29. doi: 10.1007/s11102-015-0678-x.
22. Langrand C, Bihan H, Raverot G, et al. Hypothalamo-pituitary sarcoidosis: a multicenter study of 24 patients. QJM. 2012;105(10):981-995. doi: 10.1093/qjmed/hcs121.