



ARTICLE

Ocular sarcoidosis prevalence and clinical features in the Northern Ireland population

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BACKGROUND/OBJECTIVES: To record the prevalence of ocular sarcoidosis (OS) cases present in Northern Ireland as diagnosed using the International Workshop on Ocular Sarcoidosis (IWOS) classification, 2019. There are currently no data regarding OS in this population.

SUBJECTS/METHODS: Retrospective case review of OS cases as identified by IWOS criteria 2019. Mid-year population estimates were used to calculate disease prevalence. Additional data collected included uveitis features, ocular complications and the presence of ocular only or multi-system disease.

RESULTS: A total of 86 patients were identified meeting the criteria for a diagnosis of OS, and the prevalence of OS in Northern Ireland was estimated to be 4.5 cases per 100,000. The most common type of uveitis was panuveitis in 36% of cases, and the most common ocular complication was ocular hypertension in 36% of cases and detectable glaucomatous changes in 10%. Overall, 80% of cases presenting with ocular only sarcoidosis subsequently developed second organ involvement at a rate of 14%/person-years. The most common extra-ocular site of sarcoidosis was pulmonary.

CONCLUSIONS: The Northern Ireland population has a relatively high prevalence of OS compared with other European countries. OS presenting with only ocular involvement progressed to second organ involvement in 80% of patients at a rate of 14%/person-years. Raised intra-ocular pressure with or without glaucomatous damage was a frequent finding. Thoracic CT imaging should be requested if clinical suspicion of OS exists and the presence of lymphopenia has utility in diagnosis with concurrent use of systemic ACE inhibitors.

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INTRODUCTION

Sarcoidosis is a multi-system inflammatory condition defined by the presence of non-caseating granulomata. Prevalence of the condition varies depending on region and ethnicity with the highest prevalence seen amongst African American populations followed by the Swedish population [1–3]. There is limited epidemiological literature on ocular sarcoidosis (OS) in the Irish population. The prevalence of sarcoidosis in Ireland, however, has been demonstrated to be relatively high compared to other European countries, with estimates ranging from 28.13 per 100,000 in the Republic of Ireland [4]. The prevalence of sarcoidosis across Ireland shows heterogeneity, with reported values ranging from 85 per 100,000 (in county Offaly) to 11 per 100,000 (in Northern Ireland (NI)) [4, 5]. These prevalence figures for NI may, however, be underestimated given that NI has previously been found to have the highest incidence of sarcoidosis among the UK nations of 7.7 per 100,000 person-years [5].

Ocular involvement in sarcoidosis is present in 25–70% of cases and is the presenting site of sarcoidosis in 20–40% of cases [6, 7]. Uveitis is present in ~20–30% of cases [8]. Like systemic sarcoidosis, uveitis secondary to sarcoidosis is more common in the African American population than the white Caucasian population [9], but in contrast to systemic sarcoidosis, among

the Japanese and Asian populations there is a high prevalence of OS [6, 7, 10].

Uveitis in OS may present with generic non-granulomatous features or more specific, characteristic uveitic features associated with OS such as mutton-fat KPs, iris nodules, anterior vitreous snowballs or ‘string of pearls’ and fundal findings such as punched out chorioretinal lesions and retinal vasculitis. Formal criteria for the diagnosis of OS were defined in 2009 by the first International Workshop on Ocular Sarcoidosis (IWOS) [11] and revised in 2019 [12]. In addition to the IWOS definition, there are alternative criteria that can be used clinically, e.g. Manchester Uveitis Clinic (MUC) criteria [13].

With Ireland being a region of relatively high sarcoidosis prevalence and NI the highest incidence among the UK regions, this study aimed to document the prevalence of OS cases present in the NI tertiary uveitis service as well as the clinical features present and apply current IWOS classification to this cohort. There are currently no data regarding OS in this population.

METHODS

A retrospective audit was conducted of electronic records of patients diagnosed with OS/uveitis secondary to sarcoidosis from the regional uveitis patient database at the tertiary uveitis clinic in Royal Victoria

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International Workshop on Ocular Sarcoidosis (Revised 2019) ¹³		Manchester Uveitis Clinic Criteria ¹⁴	
Definite	Biopsy Positive (any site).	Confirmed	Biopsy Positive (any site).
Presumed	No Biopsy, BHL present AND x2 Intra-ocular signs.	Presumed	Uveitis consistent with sarcoidosis. -With ACE >55 IU/L AND +ve Chest radiograph. -With ACE >100 IU/L, no chest radiograph.
Probable	No Biopsy, No BHL BUT x3 Intra-ocular signs AND x2 systemic investigations.	OR	Highly suspicious uveitis AND raised ACE OR +ve Chest radiograph AND no evidence of another cause.

Fig. 1 Diagnostic criteria for ocular sarcoidosis from the International Workshop on Ocular Sarcoidosis (2019) and Manchester Uveitis Clinic. BHL: bilateral hilar lymphadenopathy on chest radiograph, ACE: serum angiotensin converting enzyme. Intra-ocular signs: mutton-fat KPs, trabecular meshwork nodules, tented PAS, snowballs, chorioretinal peripheral lesions, periphlebitis or macroaneurysms, optic nerve/choroidal granuloma, bilaterality. Systemic investigations: BHL, negative tuberculin test/IGRA, elevated serum ACE/lysosome, lymphopenia, elevated CD4/CD8 ratio on lavage fluid, PET scan abnormalities, parenchymal lung changes.

Hospital, Belfast, NI, from 2004 to 2020. Full approval was obtained from the BHSCT Standards, Quality and Audit Department. Information was managed in accordance with the BHSCT guidance on data protection.

Included patients were those with uveitis suspected to be OS either at the time of referral to or after consultation at the Royal Victoria Hospital, Belfast. Interferon releasing assays were conducted to exclude other granulomatous disease and this was negative in all cases. In addition, all included cases had a negative non-treponemal/VDRL test.

Patient demographics were collected as well as the date and patient age at first presentation with uveitis. Clinical uveitis features were recorded for each case and classified according to the Standardization of Uveitis Nomenclature working group classification [14]. In addition, clinical investigation results were recorded including serology, biopsy and radiographic imaging. Using these data, the IWOS revised criteria (2019) [13] and MUC criteria [14] were applied to reach a diagnosis of definite, presumed and probable OS or confirmed and presumed OS, respectively, Fig. 1.

Additional data were collected on the treatment modality used in each case and complications secondary to OS. Ocular hypertension (OHT) was defined as raised intra-ocular pressure requiring treatment, and glaucoma defined as documented change of the optic disc or visual field. Whether there was only ocular or multi-system involvement (i.e. at least one further solid organ involvement) was also recorded. Among multi-system cases, it was noted whether eye involvement was a primary presentation, a concurrent presentation (OS and second organ diagnosis <1-month time period apart) or a secondary presentation (diagnosis of OS ≥ 1 month after initial solid organ diagnosis).

Serum angiotensin converting enzyme (ACE) levels were considered positive if greater than 2 standard deviations above the mean reference value for our laboratory which (>65 U/L). It was noted whether a patient was concurrently taking ACE inhibitors for systemic hypertension. Full blood counts at the time of diagnosis with uveitis were reviewed for lymphopenia defined as a lymphocyte count less than $1.0 \times 10^9/L$. Lymphocyte counts were only reviewed at the time of uveitis diagnosis and only included when no concurrent immunosuppressive medications were being taken by the patient.

Mid-year population estimates were published via the Northern Ireland Statistics and Research Agency [15]. The population of NI has also been relatively stable from 2004 to 2020 with a population change being less than 1% per year (i.e. the 2004 population estimate of 1,710,300 and the 2020 population estimate of 1,895,500). The population in NI is also unique in that immigration has, on average, been greater than emigration during the period of this study allowing patients to be followed for many years.

RESULTS

Ninety-eight patients were coded with a diagnosis of uveitis secondary to sarcoidosis in the Uveitis Database at Royal Victoria Hospital, Belfast, over a 6-year time period. When IWOS criteria were applied, 86 patients met the threshold for diagnosis of OS.

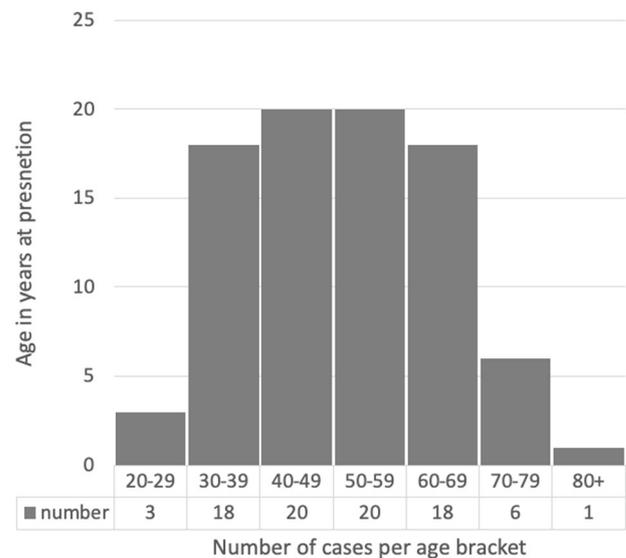


Fig. 2 Age at first presentation with uveitis consistent with ocular sarcoidosis. The distribution of ages, by decade, among study cohort at first presentation with OS.

This represents all tertiary uveitis referrals in NI. Given the latest available population estimate for NI of 1,895,500 persons, the prevalence of OS is a minimum of 4.5 cases per 100,000 population. A total of 48 patients (56%) were female and the average age at presentation was 57 years (29–82). The distribution of age at presentation (Fig. 2) shows a peak in the 5th and 6th decades. Follow up was an average 5.4 years (median 4.0 years, range 0–24 years).

There were 72 patients with bilateral uveitis (84%) and 14 patients with unilateral uveitis (16%) [9 right and 5 left eyes]. Further uveitis classification is provided in Table 1, with panuveitis as the most common site of intra-ocular inflammation in 31 patients (36%) followed by anterior uveitis in 29 patients (34%).

Intra-ocular features of OS were present in 63 cases (73%) overall (Table 1).

OHT was the most common ocular complication associated with OS and was present in 31 cases (36%) (Table 1). In 16/31 OHT cases (52%), OHT was attributed to a uveitic process (i.e. OHT at presentation with active inflammation or the presence of

Table 1. Demographics, uveitis characteristics and complications encountered for included patients with resulting IWOS and MUC classifications.

Demographics	Number of cases (percentage)
Number of cases (IWOS classification 2019)	86
Female	48 (56%)
Age (mean)	57 years
Uveitis site	
Bilateral	72 (84%)
Anterior	29 (34%)
Intermediate	20 (23%)
Posterior	6 (7%)
Panuveitis	31 (36%)
Optic nerve	1 (1%)
IWOS intra-ocular characteristics	
Mutton-fat KPs	28 (33%)
Iris Nodules	3 (3%)
Trabecular meshwork nodule/tented PAS	3 (3%)
Vitreous snowball/string of pearls	22 (26%)
Chorioretinal peripheral lesions	26 (30%)
Periphlebitis/macroaneurysms	9 (10%)
Optic nerve granuloma	1 (1%)
Ocular complications	
Cystoid macular oedema	19 (22%)
Ocular hypertension	31 (36%)
Glaucoma	9 (10%)
IWOS OS classification	
Definite	57 (66%)
Presumed	27 (31%)
Probable	2 (2%)
Unable to classify	12 (12%)
MUC classification	
Confirmed	57 (62%)
Presumed	35 (38%)
Unable to classify	5 (5%)

peripheral anterior synechiae) and in 9/31 OHT cases (29%), to a likely topical steroid responses (i.e. OHT requiring treatment associated with topical steroid use). In a further 6/31 OHT cases (19%), the cause of OHT could not be easily identified retrospectively. There were glaucomatous changes (disc and visual field changes) present in 9/86 cases (10% of all patients).

Cystoid macular oedema was present in 19/86 cases (22%), (Table 1), and was managed with topical steroid in 5 cases (6%), local steroid in 11 cases (13%) and oral steroid in 3 cases (3%).

ACE results were reviewed for all patients and were elevated (>65 U/L) in 52/86 patients (60%). Review of blood counts showed a lymphopenia present in 26/86 patients (30%) at the time of uveitis presentation (Table 2). There were 7/86 patients (8%) concurrently taking ACE inhibitors as treatment for systemic hypertension, potentially suppressing ACE levels. Of these, four patients (57%) had a lymphopenia at presentation with uveitis.

There were positive findings on chest radiography for 79/86 patients (92%). A chest CT radiograph was performed in 83 patients (87%) and signs consistent with sarcoid were reported in 76/83 cases (92%). A chest x-ray was performed on 79 patients

Table 2. Positive findings from systemic investigations and active input from multi-disciplinary team.

Bloodwork	Number of cases (percentage)
Elevated serum ACE	52 (60%)
Lymphopenia	26 (30%)
Radiology	
Positive chest x-ray findings	47 (59%)
Positive CT chest findings	76 (92%)
BHL	69 (83%)
Parenchymal lung changes	26 (31%)
PET	8 (9%)
Biopsy	
Positive biopsy	57 (66%)
Lung	33 (38%)
Skin	13 (15%)
ENT	7 (8%)
Breast	2 (2%)
Liver	2 (2%)
Groin LN	2 (2%)
Adrenal/renal	2 (2%)
Colon	1 (1%)
Lacrimal	1 (1%)
Active medical management from multi-disciplinary team	
Respiratory	66 (77%)
Dermatology	15 (17%)
ENT	10 (12%)
Cardiac	2 (2%)

(92%) and signs consistent with sarcoid were reported in 47 of 79 (59%). This demonstrates a greater sensitivity for signs of sarcoid on CT imaging than x-ray (Table 2). There were “falsely negative” reports in 25/79 chest x-rays (32%) where subsequent thoracic CT imaging did report signs consistent with sarcoidosis.

The abnormal findings on CT chest were bilateral hilar lymphadenopathy (BHL) in 69 of 83 cases (83%) and parenchymal lung changes in 26 of 83 cases (31%). Only five cases (6%) had parenchymal changes alone without BHL.

Positron emission tomography (PET) scanning was performed in 8 of 86 patients (9%), with 7 demonstrating pulmonary/mediastinal lesions and 1 demonstrating extra-pulmonary lesions. PET scanning was not requested as part of an ophthalmology work up but rather as part of a wider medical work up directed by other medical specialities.

Positive tissue biopsies from extra-ocular sites demonstrating non-caseating granuloma were present in 57/86 patients (66%). The most frequent site of a positive biopsy was from pulmonary lymph nodes, 33/86 patients (38%), followed by skin biopsies with 13/86 patients (15%). Other sites of positive biopsy are listed in Table 2.

We applied the recently updated IWOS classification (2019) for OS as an inclusion criterion for our cohort of suspected OS patients (Table 1). A total of 57 patients had a definite diagnosis (66%), 27 were presumed diagnoses (31%) and 2 were probable diagnoses (2%). A diagnostic classification could not be reached in a further 12 patients. The reason for ineligibility regarding IWOS criterion were: <2 or 3 intra-ocular signs present to meet presumed or probable diagnosis in 10 cases, and <2 systemic investigation findings present to meet a probable diagnosis in 4 cases.

Other classifications systems are used clinically, e.g. MUC classification, through which 92 patients met criteria for a diagnosis of OS (Table 1). A total of 57 cases (62%) had a biopsy confirmed diagnosis of sarcoidosis and 35 cases (38%) were presumed OS. Five cases were not classifiable under MUC classification.

OS (only) was diagnosed in 10/86 patients (12%) with multi-system in 76/86 patients (88%). Uveitis was the primary site of inflammation at diagnosis in 40/86 cases (47%) and a concurrent feature in 5/86 cases (6%). Uveitis was a secondary presentation in 31/86 cases (36%) with known systemic sarcoidosis.

Among cases with primary uveitis (40/86 cases), the mean time to second organ involvement was 9 months (median 4 months, range 1–38 months). Among patients with only ocular involvement at initial presentation (50/86 cases, i.e. excluding concurrent and secondary presentations), progression to second organ involvement was observed in 40/86 cases (80% of presentations with only ocular involvement) at a rate of 14%/person-years.

Positive tissue biopsies from solid organs are summarised in Table 2, along with the active involvement of other medical specialities. The most common extra-ocular site of sarcoid involvement was lung with 33/86 cases with positive biopsies (34%) and active respiratory physician management in 66/86 patients (77%). Other notable features were cardiac sarcoid in 2/86 patients (2%), raised or discoloured tattoos in 3/86 patients (3%) and at the time of diagnosis a concurrent or recent Bell's palsy in 11/86 patients (13%) and parotid swelling in 6/86 patients (7%).

A range of immunosuppression was used in the management of OS (Fig. 3). The most common was topical steroid, in 56/86 cases (65%), followed by systemic steroid, in 51/86 cases (59%). Eleven cases (13%) required local steroid. Treatment with antimetabolites was required in 24/86 cases (28%) and 6/86 cases (7%) required treatment with biologic agents.

DISCUSSION

There are limited data on sarcoidosis prevalence within NI and previously no published data on OS. Through review of the tertiary uveitis clinic database in the Royal Victoria Hospital, Belfast, a

minimum OS prevalence in NI of 4.5 cases per 100,000 population was found.

Demographic features were in keeping with others' findings: there was a female predominance and peak presentation was in the 5th and 6th decades. There was no bimodal distribution with a peak in younger age brackets as has been reported elsewhere [6, 10] but this reflects the predominantly Caucasian ethnicity of the NI cohort: Caucasians typically present later than African American or Asian populations [9, 10].

The characteristics of the uveitis encountered are listed in Table 1 with 84% of cases being bilateral and characteristic features of OS present in 73%. The most common sites of inflammation were panuveitis followed by anterior uveitis (36% and 34%, respectively). These uveitis characteristics are similar to a series by Ma et al. who report bilaterality in 85% of cases and the most common sites panuveitis and anterior (32% and 41% of cases, respectively), whereas Choi et al. report bilaterality in 89% of cases and intermediate and anterior as the most common sites (53% and 26%, respectively) [16, 17]. Similarities between our results and Ma et al. may be due to a relatively large number of Caucasian/European patients in both Irish and Australian population samples. When compared to Choi et al., there is less similarity in an American population in which the prevalence of African American patients would be expected to be higher.

Overall, 12% of cases experienced truly ocular only sarcoidosis leaving 88% with multi-system disease. As sarcoidosis is a multi-system disorder, it is clinically beneficial to determine the rate of disease progression to other organs following OS diagnosis. Eighty percent of ocular only cases at presentation subsequently developed second organ involvement at a rate of 14%/person-years.

This is much higher than that stated by Greon and Rothova [6]. In their review it was estimated that in ~30% of patients, uveitis may precede systemic manifestations of sarcoidosis. Equally, Ma et al. [16] describe second organ involvement, which was not present at uveitis onset, in 33% of their cohort. The larger proportion of (80%) cases in our sample in which second organ progression was observed was not due to a longer follow-up period, and our definitions of "progression" were similar to Ma et al., i.e. "not present at diagnosis of uveitis" and "greater than 1 month after diagnosis of uveitis", respectively.

The most common extra-ocular sites of sarcoidosis were pulmonary and skin involvement, seen from positive biopsy results in Table 2. Two percent of OS patients in our cohort had active cardiac sarcoidosis. These patients were investigated as they were unwell, rather than having cardiac involvement diagnosed through screening following their sarcoidosis diagnosis. It is therefore possible that the true proportion of cardiac sarcoid could be much higher, as reported by Choi et al. [17], who detected 21% with cardiac involvement through their clinic. OS patients in our clinics are now routinely referred for a cardiac consult following diagnosis.

By applying the current IWOS diagnostic classification, we were able to satisfy a diagnosis of OS in 89% of our cohort. A further 12 cases (11%) did not meet diagnostic classification due to lack of intra-ocular signs or positive systemic investigation findings and were not included in results or analysis. Two of the excluded cases were neurosarcoid with optic nerve swelling and no other intra-ocular findings and two cases were concurrently taking systemic ACE inhibitors, potentially suppressing a raised serum ACE value and preventing an OS classification. A further scenario that resulted in a questionable classification of OS using IWOS diagnostic criteria was the differentiation of "BHL" and "parenchymal changes consistent with sarcoidosis" on thoracic imaging. Although both are recognised thoracic features consistent with sarcoidosis, the latter requires additional clinical findings (i.e. one additional intra-ocular sign and two systemic investigations) in

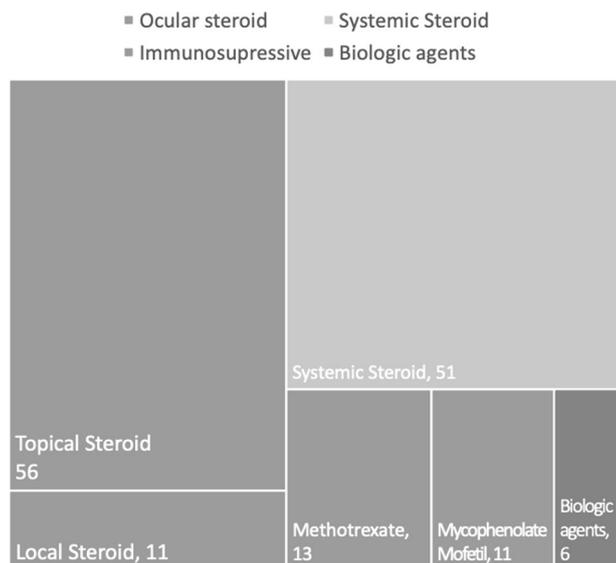


Fig. 3 Total frequency of medical agents, by category, used to treat patients with ocular sarcoidosis. The incidence of treatment modalities used among study cohort ranging from topical steroid to systemic immunosuppression.

order to be diagnosed as “probable” OS. An argument for this may be the increased frequency of BHL at presentation with sarcoidosis on thoracic imaging, compared with parenchymal changes (i.e. 25–80% vs. 10–15%, respectively) [18, 19]. BHL of course remains the classic lesion pattern described on thoracic imaging; however, parenchymal changes are not rare. Among our OS cohort, parenchymal changes were present in 30% of cases (vs. 80% with BHL) with 6% of OS cases having parenchymal changes in the absence of BHL. It is debatable whether requiring three intra-ocular signs and two systemic investigations is a relatively high threshold for diagnosis of OS when parenchymal changes are present on thoracic imaging, relative to BHL. It may be prudent to discuss imaging findings with the reporting radiologist as to gauge the nature and significance of the identified “parenchymal changes” as the description of these lesions hold “diagnostic confidence” [19]. Regardless of the nature of the positive CT findings, there is clearly high sensitivity of CT chest for sarcoidosis, and we recommend thoracic CT is essential in any cases suspicious of OS.

Chest x-ray continues to hold a role screening for OS and is recommended by the British Thoracic Society for investigating sarcoidosis, particularly when carrying out serial radiographs [20]. However, we have highlighted the increased potential for false negatives with CXR and when cases are suspicious of OS, we have always progressed to CT chest. This approach resulted in “falsely negative” chest x-ray reports in 32% of cases.

The 12 excluded patients with a suspicion of OS continue to be observed and it may be the case that these patients develop further signs that satisfy IWOS classification over time. It is worth noting that when using MUC classification, only five patients did not meet diagnostic threshold.

Where serum ACE is not raised (or suppressed through ACE inhibitor medications), clinically significant lymphopenia may be an additional serum marker or “independent predictor” for OS [13]. Jones et al. [13] describe 27% of sarcoid associated uveitis cases having lymphopenia at presentation, which compared with lymphopenia in 30% at time of presentation with uveitis in our study population. Over 50% of patients concurrently taking systemic ACE inhibitors had a lymphopenia at presentation highlighting the usefulness of this measure when ACE is suppressed medically.

The most common complication encountered was OHT, present in 36% of cases with glaucomatous changes detected in 10% of cases. In over half the OHT cases (52%), a uveitic process was identifiable as the cause and a steroid response was the likely cause in 29%. A similar proportion of OHT requiring treatment among OS patients was recorded at 34% in a Japanese population by Takahashi et al. [21] and rates of glaucoma were present in a series by Lobo et al. (11%) [22], while Edelsten et al. [23] describe slightly lower OHT rates (19%) among a UK population.

Limitations of our study are the retrospective nature of data collection, with associated reliance on clinical records, and variable follow up. In particular, some laboratory investigations are often not requested (e.g. serum lysosomes and CD4/CD8 ratio on bronchoalveolar lavage), as they require specific resources or an invasive procedure to obtain them. It is likely that the uveitis clinic in Belfast treats nearly all complex cases of OS and we expect to have detected close to all complex cases (i.e. those with intermediate or posterior segment involvement, raised intra-ocular pressure, cystoid macular oedema and cases with systemic abnormalities or investigations). This is because it is the only tertiary clinic in NI as it accepts referrals from all other ophthalmology clinics within the region. It is likely, however, that we have incomplete case capture of sarcoid related uveitis as cases may present at one of the two eye casualty clinics in the region and simple or mild cases may be managed by general ophthalmologists and not be referred to the uveitis clinic and

therefore not detected in our study. We, therefore, can describe the minimum OS prevalence in NI.

CONCLUSION

The prevalence of OS in NI is at least 4.5 cases per 100,000, which is relatively high among other European nations. Eighty percent of cases presenting with ocular only sarcoidosis subsequently developed second organ involvement and when a patient presented with only ocular involvement, second organ sarcoidosis occurred at a rate of 14%/person-years. The most common extra-ocular site of sarcoid involvement was pulmonary followed by skin, but screening is advisable for potentially serious cardiac sarcoid involvement. Thoracic CT imaging should be requested in suspicious cases given the high rate of false negatives with chest x-ray. CT parenchymal changes may be reported in the absence of lymphadenopathy. The presence of lymphopenia at presentation with OS is a useful marker for sarcoidosis and may have an increased utility in diagnosis in a population concurrently taking ACE inhibitors.

Close observation of OS cases is required with OHT, a complicating feature, in one-third of cases with detectable glaucomatous changes in 10% of patients. This was followed by cystoid macular oedema in 22% of patients.

Summary

What was known before

- A high sarcoidosis prevalence has been identified among African American and Swedish populations, while ocular sarcoidosis is more prevalent among African American and Japanese populations. There was limited literature on sarcoidosis in Ireland.
- The international workshop on ocular sarcoidosis formalised the diagnostic criteria and classification of ocular sarcoidosis enabling standardised diagnosis of the condition.

What this study adds

- We have provided data identifying a relatively high ocular sarcoidosis prevalence in the Northern Ireland population.
- We identify that 80% of “ocular only” sarcoidosis progressed to second organ involvement at a rate of 14%/person-years and prompts a multidisciplinary approach to management.
- Serum lymphopenia (when there is concurrent systemic ACE inhibitor treatment) and Chest CT were useful investigations to reach a IWOS diagnosis classification.

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AUTHOR CONTRIBUTIONS

GR was responsible for designing study, collecting data, analysing and interpreting results, writing the report and creating tables and figures. CM was responsible for designing study, collecting data, analysing and interpreting results and reviewing report. MW, GS and MC were responsible for collecting data and reviewing report.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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