

1 SUBMITTED 8 NOV 22
2 REVISION REQ. 22 JAN 23; REVISION RECD. 2 MAR 23
3 ACCEPTED 4 APR 23
4 **ONLINE-FIRST: MAY 2023**
5 **DOI: <https://doi.org/10.18295/squmj.5.2023.029>**

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7 **Incidence of Optic Neuritis Among Omani Patients with Multiple Sclerosis**
8 **at the Sultan Qaboos University Hospital, Muscat, Oman**

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15
16 **Abstract**

17 **Objectives:** Multiple sclerosis (MS) is a chronic, multifaceted, heterogeneous autoimmune
18 disease, with optic neuritis (ON) being a common early manifestation. This study aimed to
19 estimate the incidence of ON among Omani patients with MS. **Methods:** This retrospective
20 cross-sectional study included all Omani patients diagnosed with MS at the Sultan Qaboos
21 University Hospital, Muscat, Oman, between January 1991 and December 2019. Data were
22 collected from the neurology registry and electronic medical records. The data was analysed
23 descriptively using univariant and multivariant statistical techniques. **Results:** Of the 185
24 patients diagnosed with MS during the study period, 170 were included in the analysis. The
25 male-to-female ratio was 1:3 and the mean age was 28 years. The incidence of ON in the
26 population was 28.8%, with 83.7% of ON patients presenting with relapse-remitting MS
27 (RRMS). Overall, 28.6% presented with ON as an initial manifestation of MS, while 42.8%
28 developed ON at a later stage. Most patients (49.4%) were from higher-latitude regions of
29 Oman, like Muscat and Al Batinah. **Conclusion:** The incidence of both MS and ON
30 increased over the study period. While the overall incidence was low in comparison with
31 Western data, it was similar to rates reported elsewhere in the Arabian Peninsula. Overall,
32 ON was the most common manifestation of MS in the cohort, with younger female patients

33 more frequently presenting with both MS and ON. There was a significant association
34 between the RRMS subtype and ON presentation.

35 **Keywords:** Demyelinating Diseases; Optic Neuritis; Multiple Sclerosis; Multiple Sclerosis,
36 Relapsing-Remitting; Incidence; Epidemiology; Oman.

37

38 **Advances in Knowledge**

- 39 - The overall incidence of optic neuritis (ON) among patients diagnosed with multiple
40 sclerosis (MS) at a tertiary hospital in Oman over a 29-year period was 28.8%. While
41 this is lower than rates reported elsewhere around the globe, it remains in line with
42 findings reported by other Arabian Gulf countries.
- 43 - Moreover, the incidence of both MS and ON was found to increase over time,
44 particularly over the past decade, likely as a result of the application of more stringent
45 diagnostic criteria. In particular, younger female patients were more likely to present
46 with both MS and ON and there was a significant association between the relapse-
47 remitting MS subtype and ON presentation.
- 48 - The number of cases originating from the Muscat and Al Batinah regions of Oman
49 supports the hypothesis that latitude affects MS incidence.

50

51 **Application to Patient Care**

- 52 - As the findings show that ON is a common early manifestation of MS in Omani
53 patients, ophthalmologists and family physicians should ensure that they refer patients
54 presenting with symptoms of vision loss for neurological assessment, especially
55 young female patients who are at greater risk of developing both ON and MS.
- 56 - Moreover, in light of the fact that the incidence of both MS and ON increased
57 considerably over the study period, there is a need for enhanced suspicion of MS in
58 the differential diagnosis process. Moreover, a national MS-specific registry should
59 be established to more accurately monitor the number of cases recorded every year.

60

61 **Introduction**

62 Multiple sclerosis (MS) is a chronic, multifaceted, complicated, and heterogeneous
63 autoimmune disease which results in central nervous system inflammation, demyelination,
64 gliosis, and axonal degeneration.¹ Neurological deficits are common due to interrupted
65 communication between neurons in the brain and spinal cord as a result of the demyelination
66 process. Clinically, MS takes a variety of forms which can be distinguished through disease

67 activity and patterns of relapse and remission.¹ According to current international
68 classifications, four MS subtypes are recognised: relapsing-remitting MS (RRMS), primary
69 progressive MS, secondary progressive MS (SPMS), and progressive-relapsing MS.² The
70 primary cause of MS is still unknown, although both environmental and genetic factors are
71 believed to play a role. The epidemiology of MS varies according to demographic
72 characteristics and latitude, a well-established risk factor; in addition, ethnicity/race has also
73 been found to influence the global distribution of MS.³

74
75 Optic neuritis (ON) is an acute, inflammatory, demyelinating disease of the optic nerve
76 resulting from an autoimmune process, characterised by unilateral, painful, and rapid loss of
77 vision.^{4,5} Typically, ON is recognised as an early clinical manifestation of MS in 20% of
78 patients, but this condition can occur over the course of the disease in up to 50% of all MS
79 patients.⁶ In particular, female patients between 18–45 years of age have an increased
80 tendency to develop ON in comparison to other MS patients.⁷ This study aimed to estimate
81 the incidence of ON among Omani patients diagnosed with MS at a tertiary hospital over a
82 29-year period and compare the findings to internationally published data.

83 84 **Methods**

85 This retrospective cross-sectional study was conducted at the Sultan Qaboos University
86 Hospital (SQUH), a tertiary hospital in Muscat, Oman, from January 1991 until December
87 2019. This study included all Omani patients seen at SQUH with confirmed MS diagnoses
88 according to the 2017 McDonald diagnostic criteria.⁸ Patients without confirmed MS
89 diagnoses were excluded from the study. Data were collected from the SQUH neuro-
90 ophthalmology clinic registry, the patients' electronic medical records, and the hospital
91 information system database.

92
93 Electronic medical records were established at SQUH in 2006; as such, the data of patients
94 diagnosed with MS prior to 2006 were retrieved from the hospital's neurology clinic registry,
95 while data from 2006 onwards were collected from the patients' electronic medical records
96 (TrakCare®, InterSystems Corp., Cambridge, Massachusetts, USA). Various information
97 was recorded, including sociodemographic characteristics (i.e., age, gender, and location of
98 residence), year of diagnosis, subtype of MS, and the presence of ON. In addition, additional
99 data were collected and reported for patients with ON, including age at presentation, number
100 of attacks during follow-up period, and progression of the disease. Patients were contacted

101 directly to confirm their location of residence in order to estimate the geographic distribution
102 of the disease.

103

104 Collected data were analysed using the Statistical Package for the Social Sciences (SPSS),
105 Version 23 (IBM Corp., Armonk, New York, USA). Ethical approval for this study was
106 obtained from the Medical Research & Ethics Committee of the College of Medicine &
107 Health Sciences at Sultan Qaboos University. Further authorisation was obtained from the
108 relevant hospital authorities to access the patients' electronic medical records and the hospital
109 information system database.

110

111 **Results**

112 A total of 185 patients were diagnosed with MS at SQUH between January 1991 and
113 December 2019; of these, 15 patients (8.1%) were excluded due to diagnostic uncertainty,
114 resulting in a 170 patients (85.4%) being included in the analysis. Overall, 59 (34.7%) were
115 male and 111 (65.3%) were female, with a male-to-female ratio of 1:3 and a mean age of 28
116 years. The youngest patient began showing signs of MS at the age of 9 years, whereas the
117 eldest was 60 years old. In terms of subtype, most patients had RRMS (n = 135; 79.4%),
118 followed by clinically isolated syndrome (CIS; n = 21; 12.4%), and SPMS (n = 14; 8.2%).
119 Other MS subtypes were not detected or diagnosed during the study period.

120

121 Of the 135 patients with RRMS, 50 were male (37%) and 85 were female (63%), while there
122 were six male (28.6%) and 15 female (71.4%) patients with CIS, and three male (21.4%) and
123 11 female (78.6%) patients with SPMS [Figure 1A]. The association between gender and MS
124 subtype was not significant ($P > 0.050$). The first documented case of MS in the neurology
125 registry was recorded in 1991. Subsequently, the number of MS diagnoses per year began to
126 increase, particularly from 2010 onwards. The greatest number of cases per year was
127 recorded in 2016 (n = 23), comprising six male (26.1%) and 17 female (73.9%) patients
128 [Figure 1B].

129

130 In terms of geographic distribution, the majority of MS patients originated from Muscat (n =
131 48; 28.2%) [Figure 1C], with 16 male (33.3%) and 32 female (66.7%) patients, followed by
132 Al Batinah (n = 36; 21.2%), with seven male (19.4%) and 29 female (80.6%) patients. The
133 region with the fewest cases was Ad Dhakhiliyah (n = 16; 9.4%), of which six patients
134 (37.5%) were male and 10 (62.5%) were female. No cases were reported from three

135 governorates of Oman (Musandam, Al Buraimi, and Al Wusta) [Table 1]. The association
136 between disease incidence and areas of high latitude was not significant ($P > 0.050$).

137

138 Over the 29-year study period, 49 MS patients developed ON, resulting in an incidence of
139 28.8%; of these, 11 patients (22.5%) were male and 38 (77.5%) were female [Figure 2A].

140 The first case of ON at SQUH appeared in the registry in 2004, with the number of diagnoses
141 per year increasing considerably from 2012 onwards. The highest number of cases was
142 reported in 2016 for male patients ($n = 2$) and 2017 for female patients ($n = 7$) [Figure 2B].

143 Overall, 28.6% of patients with both MS and ON presented with ON as an initial presentation
144 of MS, while 42.8% developed ON over the course of the disease [Table 2]. The association
145 between gender and the development of ON was not significant ($P = 0.050$); however, there
146 was a significant association with MS subtype ($P < 0.050$), with the majority of ON cases
147 occurring in patients with the RRMS subtype (83.7%) [Table 3].

148

149 **Discussion**

150 The incidence of ON among MS patients at SQUH over the 29-year study period was 28.8%,
151 lower than rates reported elsewhere around the world. According to a prospective study
152 conducted in India, the incidence of ON among MS patients was 70% ($n = 20/30$).⁹ Another
153 study reported an incidence of 50% at a tertiary care unit in Turkey, with ON often reported
154 as an initial presenting feature of MS.¹⁰ The low incidence rate of ON noted in the current
155 study could be due to several reasons, including methodological differences in sample size
156 and study design, as well as genetic variations between different populations.

157

158 However, it is also possible that this finding is due to the generally low incidence of MS in
159 Oman, given the previously reported prevalence rate of 4 in 100,000 individuals.¹¹ Other
160 Arabian Gulf countries have reported similarly low rates of MS, although there are
161 methodological concerns to such studies which may hinder definitive conclusions as to
162 regional prevalence.¹² A more recent study indicated that the rate of MS in Oman may be
163 much higher than previously believed, with a crude estimated prevalence of 15.9 per 100,000
164 individuals, designating the country as a medium-risk zone.¹³

165

166 In the present study, the incidence of both MS and ON at SQUH was found to increase
167 considerably over time, beginning from 2010–2012 onwards. This increase over the past
168 decade may be due to the application of the McDonald criteria to support the diagnosis of

169 suspected cases of MS at SQUH, resulting in fewer cases going undiagnosed.⁸In the present
170 study, ON represented the first clinical manifestation of MS in 28.6% of patients who
171 developed ON. This finding is in parallel with other research conducted elsewhere around the
172 globe. In Bosnia and Herzegovina, 10 out of 89 MS patients (11.2%) demonstrated clinical
173 signs of ON as the first sign of disease, a finding which was statistically significant compared
174 to other disease manifestations ($P = 0.01$).⁷ In addition, a previous review of the literature
175 suggested that ON is the initial presentation in approximately 20% of MS patients.¹⁴

176

177 Overall, 79.4% of MS patients in the present study had the RRMS subtype, while the
178 remaining 12.4% and 8.2% of patients had CIS and SPMS, respectively. A retrospective
179 study conducted in the United Arab Emirates (UAE) reported a comparable distribution of
180 these subtypes among Emirati MS patients (77.8%, 12.3%, and 8.2%, respectively).¹⁵
181 Moreover, there was a significant association between the RRMS subtype and ON
182 presentation in the current Omani cohort, with 83.7% of patients with both ON and MS
183 having the RRMS subtype; this result was found to be slightly higher in comparison to other
184 research reporting that 70% of MS patients with ON demonstrated relapsing-remitting
185 disease activity.¹⁶ In addition, female patients were found to be more frequently diagnosed
186 with MS compared to male patients in the present study, at a ratio of 1.9. The gender ratio of
187 MS cases varies depending on country and region, with higher ratios of 2.6 and 3.0 reported
188 in the USA and East Asia, respectively.¹⁷ In turn, the female preponderance of MS is lower in
189 Arabian Gulf countries, with ratios of 1.8 and 1.3 reported in Kuwait and Saudi Arabia,
190 respectively.^{17,18} In the present study, 34.2% of female patients with MS developed ON
191 compared to 18.6% of male patients, with a female-to-male ratio of 3.5. The female
192 predominance of ON is well-established in the existing literature at a ratio of 3 or higher.¹⁹

193

194 In the present study, the mean age of the enrolled population was 28 years, with similar mean
195 ages observed for both males and females at 29 and 28 years, respectively. Corresponding
196 findings have been reported from Iran (mean age: 25 years), while MS patients in the UAE
197 are reportedly somewhat older (mean age: 34 years).^{15,20} In turn, the mean age of ON patients
198 in the current research was found to be 26 years, with a mean age of 24 and 27 years for male
199 and female patients, respectively. Overall, the majority of ON patients (59.2%) were between
200 21–30 years of age. This finding was lower in comparison with data originating from Hong
201 Kong showing the mean age of ON patients to be 40 years; however, 90% of MS patients
202 presenting with ON in Bosnia and Herzegovina were between 18–30 years of age.^{7,21} Such

203 results suggest that the demographic epidemiology for MS-associated ON may be similar to
204 that of MS in general.

205

206 Latitude is a well-established factor affecting the incidence of both MS and ON; for instance,
207 previous research has indicated that the incidence of MS in Argentina is six times higher than
208 that recorded in Ecuador.²² It is therefore unsurprising that Oman, a country located in the
209 East Mediterranean region, should demonstrate a lower incidence of MS compared with
210 Western countries of higher latitude.²³ Moreover, according to the geographical distribution
211 of patients in the present study, certain regions of Oman at higher latitudes (i.e., Muscat and
212 Al Batinah) accounted for the greatest number of patients, with fewer cases originating from
213 lower-latitude regions like Dhofar, Ash Sharqiyah, Ad Dhakhiliyah, Ad Dhahirah, and Al
214 Wusta.

215

216 Nonetheless, the association between latitude and disease incidence was not statistically
217 significant in the present study, which may be due to several reasons. First, no cases were
218 reported from the highest-latitude areas in Oman (Musandam and Al Buraimi). Second, such
219 associations are difficult to ascertain in a single country that does not span a considerable
220 latitude or longitude. Finally, as the capital city of Oman, Muscat is home to a large
221 proportion of the national population, followed by the surrounding region of Al Batinah,
222 which may account for the large number of cases from these areas. However, it was found
223 that male patients more frequently originated from areas of lower latitude like Dhofar
224 compared with other governorates. The idea that the gender ratio in MS may vary with
225 changes in latitude might be another possible explanation for these findings.²⁴

226

227 Interpretation of the findings of this study is contingent upon certain limitations.

228 Generalisation of the results is difficult as the study was conducted using a retrospective
229 cross-sectional design and was limited to a single institution. While SQUH is a tertiary care
230 institution which accepts referrals from all over the country, the catchment area remains
231 limited; moreover, the presence of other tertiary institutions in Muscat which might also
232 receive MS and ON patients prohibits generalisation of the incidence of these conditions to
233 the whole of Oman. In addition, as a partially heritable disease, genetic factors play a
234 considerable role in the epidemiology and incidence of MS. Unfortunately, data concerning
235 such genetic factors were missing for the majority of patients in the present study. Further

236 prospective research is therefore recommended to counteract these limitations using a larger
237 sample size.

238

239 **Conclusion**

240 Over the 29-year study period, the incidence of ON among MS patients at SQUH was low
241 (28.8%), a rate in keeping with other Arabian Gulf countries. Nonetheless, ON remained the
242 most common early manifestation of MS among the enrolled patients, with almost one-third
243 of MS patients presenting initially with ON as their first symptom. Moreover, the incidence
244 of both MS and ON appeared to increase over time, particularly over the last decade,
245 supporting the need for further research on this topic. Finally, more MS cases were reported
246 from higher-latitude areas of Oman, a result in line with previous research supporting latitude
247 as a well-established risk factor for MS.

248 Further research is needed that can focus on more in-depth analysis such as comparing the
249 difference between the initial presentation (ON versus other MS) and gender, governorate
250 and year and whether sub-types (RRMS vs other sub-types) are significantly different by
251 gender, governorate and year.

252

253 **Authors' Contribution**

254 AM designed the study. FK and BS collected the data. FK performed the statistical analysis.
255 FK and BS drafted the manuscript. AM critically reviewed and revised the manuscript. All
256 authors approved the final version of the manuscript.

257

258 **Conflict of Interest**

259 The authors declare no conflicts of interest.

260

261 **Funding**

262 No funding was received for this study.

263

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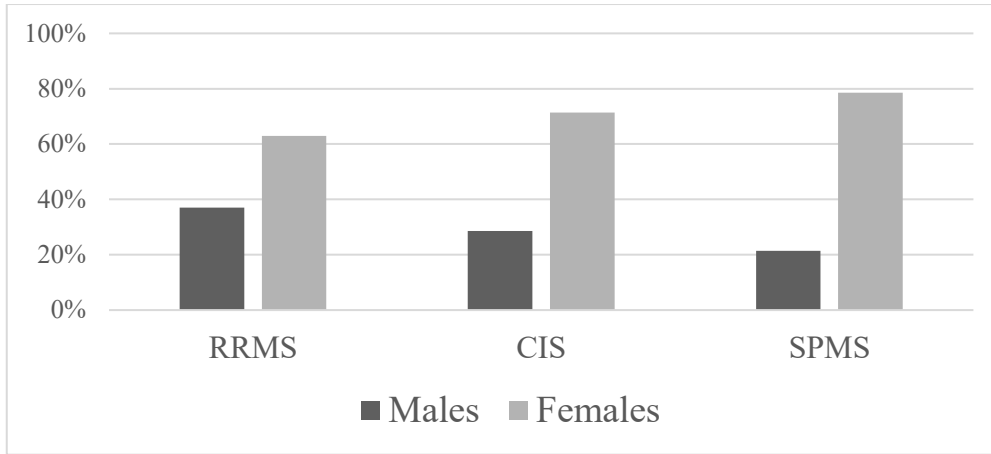
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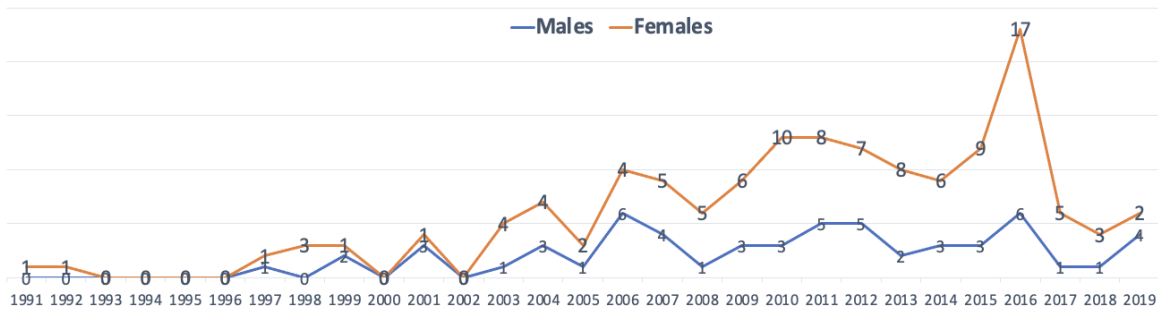
Figure 1A



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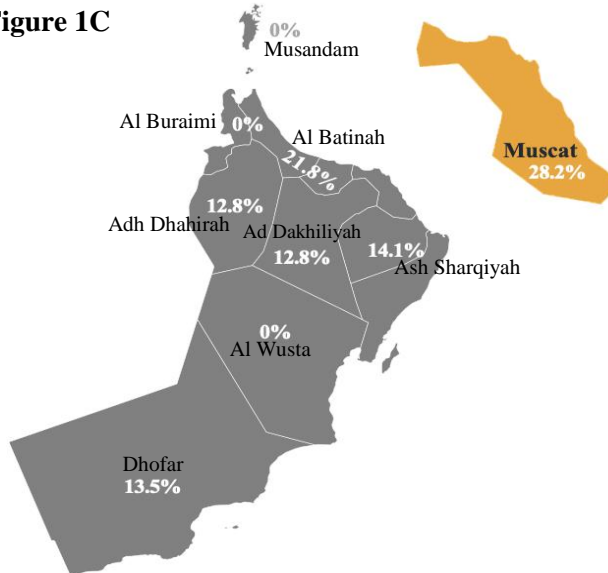
Figure 1B



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Figure 1C



334 **Figure 1:** Distribution of multiple sclerosis (MS) cases according to gender by (A) subtype,

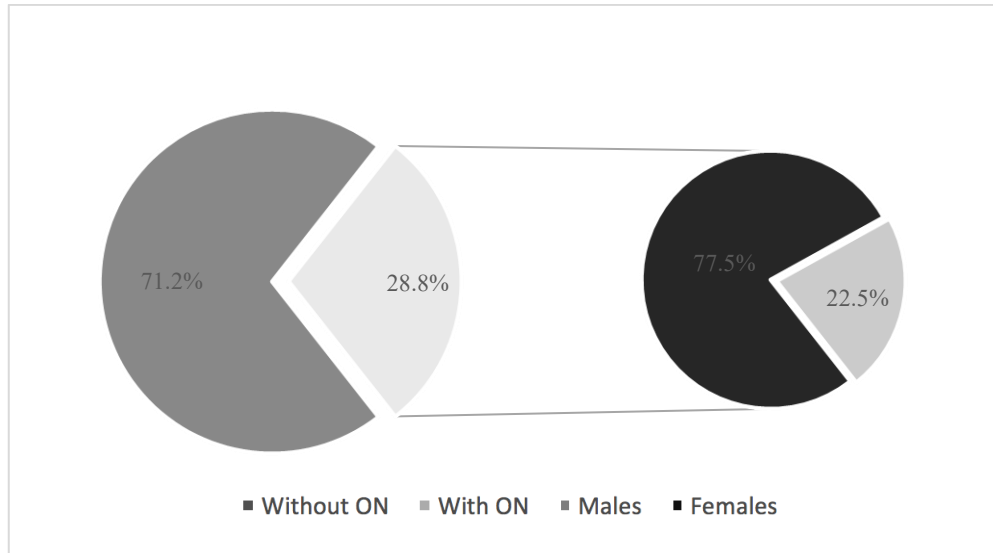
335 (B) over time at the Sultan Qaboos University Hospital, Muscat, Oman, from 1991–2019 (N =

336 170) and (C) among governorates.

337 *SPMS = secondary progressive multiple sclerosis; CIS = clinically isolated syndrome; RRMS*
 338 *= relapse-remitting multiple sclerosis.*

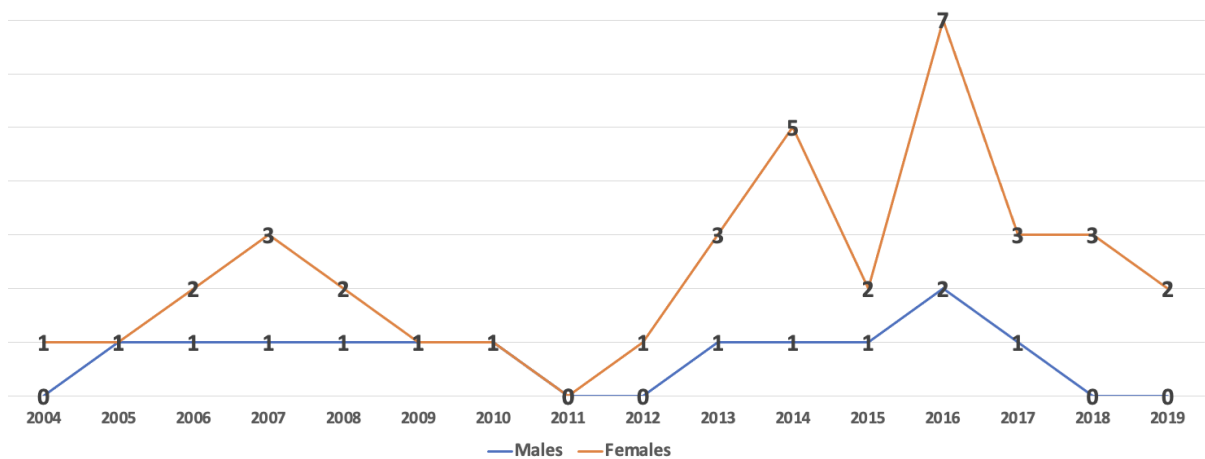
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Figure 2A



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Figure 2B



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Figure 2: Distribution of combined optic neuritis and multiple sclerosis cases by (A) gender and (B) over time at the Sultan Qaboos University Hospital, Muscat, Oman, from 2004–2019 (N = 49).

ON = optic neuritis.

352 **Table 1:** Regional distribution of multiple sclerosis cases according to gender at the Sultan
 353 Qaboos University Hospital, Muscat, Oman, from 1991–2019 (N = 170)

Governorate	Gender, n (%)		
	Male	Female	Total
Muscat	16 (33.3)	32 (66.7)	48 (28.2)
Al Batinah (North and South)	7 (19.4)	29 (80.6)	36 (21.2)
Dhofar	12 (48)	13 (52)	25 (14.7)
Ash Sharqiyah (North and South)	8 (33.3)	16 (66.7)	24 (14.1)
Ad Dhahirah	10 (47.6)	11 (52.4)	21 (12.4)
Ad Dhakhiliyah	6 (37.5)	10 (62.5)	16 (9.4)
Musandam	0 (0)	0 (0)	0 (0)
Al Buraimi	0 (0)	0 (0)	0 (0)
Al Wusta	0 (0)	0 (0)	0 (0)
Total	59 (34.7)	111 (65.3)	170 (100)

354
 355 **Table 2:** Initial presentation of combined optic neuritis and multiple sclerosis cases by gender
 356 at the Sultan Qaboos University Hospital, Muscat, Oman, from 1991–2019 (N = 49)

Gender	Initial presentation, n (%)			
	ON	Other MS manifestations	Both	Total
Male	2 (18.2)	3 (27.4)	6 (54.5)	11 (22.4)
Female	12 (31.6)	18 (47.4)	8 (21.1)	38 (77.6)
Total	14 (28.6)	21 (42.8)	14 (28.6)	49 (100)

357 *ON = optic neuritis; MS = multiple sclerosis.*

358
 359 **Table 3:** Incidence of combined optic neuritis and multiple sclerosis (MS) cases according to
 360 gender and MS subtype at the Sultan Qaboos University Hospital, Muscat, Oman, from 2004–
 361 2019 (N = 49)

Gender	MS subtype, n (%)			
	RRMS	CIS	SPMS	Total
Male	10 (90.9)	1 (9.1)	0 (0)	11 (22.4)
Female	31 (81.6)	4 (10.5)	3 (7.9)	38 (77.6)
Total	41 (83.7)	5 (10.2)	3 (6.1)	49 (100)

362 *MS = multiple sclerosis; RRMS = relapse-remitting multiple sclerosis; CIS = clinically*
 363 *isolated syndrome; SPMS = secondary progressive multiple sclerosis.*

364