Respiratory Medicine 160 (2019) 105753

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Correspondence

Correspondence for "Clinical epidemiology of familial sarcoidosis: A systematic literature review"

Author reply:

We appreciate the correspondences of Rossides and colleagues [1] and Calender and colleagues [2] related to our literature review on the clinical epidemiology of familial sarcoidosis [3], the goal of which was to bring together scattered and sometimes paradoxical data on the clinical epidemiology of familial sarcoidosis.

Heritability. As described, our systematic literature search was run on March 20, 2017 and this was indeed before the publication of the interesting article by Rossides and coworkers [4]. In their recent family study [4], they used high quality data from Swedish population-based registers, including the National Patient Register (NPR), and the Multi-Generation Register (MGR). The authors estimated a heritability for sarcoidosis of 39% (95% CI 12–65%) [4].

Heritability can vary between populations and can change over time as circumstances change [5]. This is illustrated by earlier work of the Swedish group [6]: based on the Swedish NPR, the authors presented prevalence estimates of sarcoidosis in Sweden which varied widely by Swedish county. Disease prevalence ranged from 105 to 278 per 100 000, with the highest observed in some less densely populated areas of Sweden in the northwest. They suggested that the observed geographical variation might be explained by a disease associated exposure more common in rural areas, or by differences in the genetic composition of the individuals from different more or less ethnically diverse regions in Sweden [6]. Similar factors influence estimates of heritability, it is thus likely that each new study, with different study populations, even when using similar methodologies, will yield different results. Therefore, it is all the more striking that previously reported heritability estimates by differently designed studies, and importantly in different study populations, were 60% (± 17) to 70% (± 12) [7] and 66% (95% CI 45%–80%) [8]. The confidence intervals from the three studies in which heritability was estimated [4,7,8] overlap and agree on the point that there is significant heritability in sarcoidosis.

Prevalence of familial disease. Our systematic literature search selected 27 articles out of the 459 retrieved by the search at first instance. Many studies did not address familial sarcoidosis and could not be included in the pooled prevalence estimate. We have sought to summarize the literature findings on familial sarcoidosis, because we support its study, for the clinical and etiological importance.

We ourselves were initially surprised by the high number of familial sarcoidosis cases in the French study, and in a personal communication asked the first author if there was a bias in the inclusion of the familial cases. The answer was negative, and therefore we decided to include the study. The clarification of the French study by Calender and colleagues [2] shows that this was a misunderstanding. There was indeed no bias in the inclusion of familial cases, but there was a bias towards inclusion of cases with familial sarcoidosis versus non-familial cases. This means that the pooled prevalence of familial sarcoidosis that we calculated [3] is biased. To assess the extent of bias in our findings, we have recalculated the pooled prevalence of familial sarcoidosis. The estimate for the pooled prevalence of familial sarcoidosis in the review was 9.5% (CI 4.6–16.1) [3]; without the French study [9] it is 7.3% (CI 4.1–11.4; random effects model). Rossides and colleagues recently found a prevalence of familial sarcoidosis of approximately 4.1% [1,4]. Considering these findings, it is clear that familial aggregation of sarcoidosis exists, although the prevalence will vary between populations.

Most importantly, disease in relationships-by-marriage have been reported scarcely [10–12]. In the ACCESS study the relative risk for spouses was not increased [10]. Still, examples of such relationships are: the occurrence of Löfgren's syndrome in sisters-in-law [11], and a husband and wife, possibly with Löfgren's syndrome as well, sharing an identical HLA-haplotype [12]. Löfgren syndrome is an acute form of sarcoidosis characterised by erythema nodosum, bilateral hilar lymphadenopathy (BHL), and bilateral ankle arthritis or periarticular inflammation [13]. Although the trigger is unknown disease occurrence is seasonal and disease susceptibility is highly dependent on carriership of common HLA genotypes [13]. This illustrates that risk estimates may not only vary by population but may even vary by sarcoidosis disease phenotype. Relationships-by-marriage in the occurrence of sarcoidosis have not been studied extensively, but would be highly informative. Moreover, research for relative risks in second- and third-degree relatives is needed. Finally, it is unknown whether familial risk studies should be limited to sarcoidosis or should involve the entire spectrum of immune-mediated diseases. We have complemented our first review with a review on clustering of immune-mediated diseases in sarcoidosis [14] and found that clustering of sarcoidosis and other immune-mediated diseases in patients and their relatives frequently occurs.

By reviewing what is known on familial disease in sarcoidosis we aim to provide patients and care professionals with information. "Why do *I* have sarcoidosis?" and "will my family members also develop disease?" are some of the most frequently asked questions by patients. A survey on research prioritization conducted during a patient meeting at our institute showed that research on familial sarcoidosis and heritability was prioritized by 69% of patients with sarcoidosis and their family members.

From the present study [3] we can conclude that familial sarcoidosis exists but varies between populations and that relatives have increased risks for sarcoidosis. Further research is needed to obtain more precise familial relative risk estimates (especially for relationships-by-marriage, second, and third degree relatives), and to identify clinical phenotypes associated with familial disease. Hopefully this will eventually contribute to the understanding of the aetiology of sarcoidosis, and improve the care for patients and their families.

Declaration of interests

None.

https://doi.org/10.1016/j.rmed.2019.07.012

Available online 10 July 2019

References

[1] M. Rossides, J. Grunewald, A. Eklund, S. Kullberg, J. Askling, E.V. Arkema, Correspondence for “Clinical epidemiology of familial sarcoidosis: a systematic literature review, Respir. Med. (2019 May 13).

[2] A. Calender, D. Valeyre, D. Israel-Biet, Y. Pacheco, Correspondence for "clinical epidemiology of familial sarcoidosis: a systematic literature review", Respir. Med. (2019 Jun 10).

[3] M. Terwiel, C.H.M. van Moorsel, Clinical epidemiology of familial sarcoidosis: a systematic literature review, Respir. Med. 149 (2019 Mar) 36–41.

[4] M. Rossides, J. Grunewald, A. Eklund, S. Kullberg, D. Di Giuseppe, J. Askling, et al., Familial aggregation and heritability of sarcoidosis: a Swedish nested case – control study, Eur. Respir. J. 52 (2) (2018 Aug) 1800385.

[5] A. Tenesa, C.S. Haley, The heritability of human disease: estimation, uses and abuses, Nat. Rev. Genet. 14 (2) (2013 Feb 18) 139–149.

[6] E.V. Arkema, J. Grunewald, S. Kullberg, A. Eklund, J. Askling, Sarcoidosis incidence and prevalence: a nationwide register-based assessment in Sweden, Eur. Respir. J. 48 (6) (2016 Dec) 1690–1699.

[7] V.E. Headings, D. Weston, R.C. Young, R.L. Hackney, Familial sarcoidosis with multiple occurrences in eleven families: a possible mechanism of inheritance, Ann. N. Y. Acad. Sci. 278 (1 Seventh Inter) (1976 Sep) 377–385.

[8] A. Sverrild, V. Backer, K.O. Kyvik, J. Kaprio, N. Milman, C.B. Svendsen, et al., Heredity in sarcoidosis: a registry-based twin study, Thorax 63 (10) (2008 Oct 1) 894–896.

[9] Y. Pacheco, A. Calender, D. Israël-Biet, P. Roy, S. Lebecque, V. Cottin, et al., Familial vs. sporadic sarcoidosis: BTNL2 polymorphisms, clinical presentations, and outcomes in a French cohort, Orphanet J. Rare Dis. 11 (1) (2016 Dec 3) 165.

[10] B.A. Rybicki, M.C. Iannuzzi, M.M. Frederick, B.W. Thompson, M.D. Rossman, E.A. Bresnitz, et al., Familial aggregation of sarcoidosis, Am. J. Respir. Crit. Care Med. 164 (11) (2001 Dec 1) 2085–2091.

[11] E. Fité, J.M. Alsina, J.M. Antó, J. Morera, Sarcoidosis: family contact study, Respiration 65 (1) (1998) 34–39.

[12] J. Elford, P. Fitch, E. Kaminski, C. McGavin, I.P. Wells, Five cases of sarcoidosis in one family: a new immunological link? Thorax 55 (4) (2000 Apr 1) 343–344.

[13] B. Karakaya, Y. Kaiser, C. van Moorsel, J. Grunewald, Löfgren’s syndrome: diagnosis, management, and disease pathogenesis, Semin. Respir. Crit. Care Med. 38 (04) (2017 Aug 27) 463–476.

[14] M. Terwiel, J.C. Grutters, C.H.M. van Moorsel, Clustering of immune-mediated diseases in sarcoidosis, Curr. Opin. Pulm. Med. (2019 Jun 18) 1.

Michelle Terwiel, Coline H.M. van Moorsel*

Department of Pulmonology, St Antonius ILD Center of Excellence, St Antonius Hospital, Nieuwegein, the Netherlands

E-mail address: c.van.moorsel@antoniusziekenhuis.nl (C.H.M. van Moorsel).

* Corresponding author.