Reviewer's report

Title: Incidence of hereditary amyloidosis and autoinflammatory diseases in Sweden: endemic and imported diseases

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Reviewer: Tom Pettersson

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The aim of this study was to investigate the incidence of neuropathic amyloidosis and familial autoinflammatory diseases (with a potential of being complicated by amyloidosis) in Sweden over the years 2001-2008. Patients with a diagnosis of neuropathic heredofamilial amyloidosis (presumably mostly familial ATTR amyloidosis) or non-neuropathic heredofamilial amyloidosis (presumably mostly familial Mediterranean fever (FMF) with or without amyloidosis) were identified using data from the Swedish Hospital Discharge Register and Outpatient Register. The investigators reached the number of 2.02 per million for neuropathic heredofamilial amyloidosis and 2.83 per million for non-neuropathic heredofamilial amyloidosis. Most of the patients with the former diagnosis came from two northern counties of Sweden, whereas the great majority of patients bearing the latter diagnosis were immigrants, or descendants of immigrants, principally from the eastern Mediterranean area. Pooling of data concerning the two diagnoses gave an overall standardized incidence rate of 5.12 per million.

I have some questions and comments regarding the manuscript:

Concerning neuropathic heredofamilial amyloidosis: The rather high age at diagnosis indicates that only patients with clinically overt amyloidosis have been included but to what extent have the authors made sure that this diagnostic category does not include persons with transthyretin mutations but without symptoms? Including them would significantly increase the incidence rates.

I question the value of pooling data of neuropathic amyloidosis and autoinflammatory diseases in order to reach an “overall incidence rate”. These disease categories differ pathogenetically very much from one another and they have completely different amyloid precursor proteins. Moreover, in the former disease category amyloidosis would be expected to be present when the diagnosis is made, whereas amyloidosis is only a potential complication in the diseases of the latter category. I suggest that the authors leave out the data concerning pooling of the different disease categories. Admittedly, one the whole I would hesitate to include incidence data on both ATTR amyloidosis and autoinflammatory diseases in the same article, but I have no major objections against the structure of the study.

Minor comments

On page 4 the authors should specify that serum amyloid A (SAA) is the very
amyloid precursor in reactive amyloidosis. The expression “serum acute phase proteins” is simply not accurate enough.

On page 5 the expression “1049 monogenic patients” should be changed to “1049 patients with monogenic diseases”.

On page 5 the authors mention kidneys and gastrointestinal tract as being vulnerable organs in FMF. This may be misleading unless they specify that this is the case if the patients have developed amyloidosis.

The sentence on page 6 “Although amyloidosis diagnosis should be based …” is not readily comprehensible and should be rewritten.

Page 10, Discussion, 2nd sentence: The correct term is immunoglobulin light chain amyloidosis, not “immunoglobin light chain amyloidosis”.

Page 11: Although FMF is found mostly in Turks, Armenians, Arabs and non-Ashkenazy Jews, the disease it is not “always restricted” to these ethnicities. Another expression, for example “almost always restricted” would be preferable. And the authors may wish to amend the phrase “no case have been described in Scandinavia” to, for example “no cases have been described in individuals of Scandinavian origin”.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I declare that I have no competing interests