Letters to the Editor

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Rheumatoid arthritis in β-thalassaemia trait

SIR, We read with great interest the letter by Montecucco *et al.* [1]. They concluded that subjects with the β-thalassaemia (β-thal) trait have a high prevalence of polyarthritis resembling rheumatoid arthritis (RA), but not of other inflammatory rheumatic diseases, such as connective tissue disease and seronegative spondyloarthrytis. They also stated that the so-called arthritis of the β-thal trait is probably not a distinct clinical entity, as previously thought, and may be regarded as a mild form of seronegative RA. We reached the same conclusion in our own studies of this topic.

In our original report, published in 1975 [2], we studied the incidence of the β-thal trait (confirmed by haemoglobin electrophoresis) in 146 RA patients consecutively admitted to the hospital, and compared it with that of the control population of the Ferrara and Rovigo areas of Italy, where the prevalence of thalassaemia is high. We found a significant increase in thalassaemia in a rheumatoid series. The frequency of the β-thal trait reached 19.8% among patients with RA compared with 13.4% and 11.3% in the random population of the same two areas, respectively, and was 1.5 times greater than the expected prevalence rate of 13.1%.

In the series described by Montecucco *et al.* the frequency of the β-thal trait in RA patients is also elevated (three times higher than the expected frequency), reaching the 6.4% in RA patients compared with 2.1% of the control population, taking the inpatients of the general medicine department as the control population. This may be misleading, because β-thalassaemic subjects can be considered as a population with its own biology, which is still not fully understood. It is well known that β-thal exerts a protective or a facilitating role in certain diseases: in particular, individuals with the β-thal trait are more resistant to malaria, tubercolosis and essential hypertension and more susceptible to gastroduodenal ulcers and liver cirrhosis than non-thalassaemic subjects [3]. For this reason, the hospitalized control population can be considered a selected population. Surprisingly, but in agreement with previous data [4], we found a lower frequency of the β-thal trait in patients affected with other connective tissue diseases. Among 240 lupus patients living in the Ferrara and Rovigo areas, the frequency of the β-thal trait was 4%, which is much lower than the 13% prevalence of the trait in the control population (unpublished data). We still have no explanation for these data.

There have been few studies of the immunological reactivity of heterozygous β-thal subjects. In 1985 we demonstrated a different behaviour of circulating T-cell subpopulations in RA patients with and without β-thal. RA patients without β-thal had more active T-cells than patients with β-thal [5, 6]. We concluded that β-thal may modify the immunological profile of circulating T cells in patients with RA through a different background immune reactivity. Further studies with more modern techniques concerning T-cell subpopulations and their functions will be necessary to determine whether β-thal subjects have a specific T-cell defect related to the aetiopathogenesis of RA. Studies exploring polymorphonucleate functions have not shown any particular alteration [7].

As Montecucco *et al.* suggested, another interesting issue is whether RA patients with β-thal have a particular HLA haplotype. In order to investigate this relationship, we studied the frequency of class II HLA antigens DR1, 2, 3, 4, 5 and 7 in 59 RA subjects (28 of whom had β-thal) matched with a control population of 71 normal subjects. We did not find any significant difference between the probands and the controls [8].

In 1984 we conducted another study in 58 RA β-thal patients (12 males and 46 females, average age 56.4 yr, mean duration of disease 6.8 yr) to assess if there were clinical differences compared with RA patients without the β-thal trait [9]. The onset, course, type and severity of joint involvement and clinical features did not differ significantly between the two groups. However, we obtained some noteworthy results. There was a reduction in the number of the systemic complications that are usually seen in RA, in particular of rheumatoid nodules, in β-thal carriers, and there was a more severe degree of osteoporosis and a lower value of ESR (related to the severity of the disease) in β-thal RA patients compared with non-β-thal RA patients.

On the basis of our data we conclude that subjects with the β-thal trait have a higher prevalence of a mild form of RA compared with the normal population. The way in which the β-thal trait interferes with the appearance of RA remains a matter of speculation. It may be related to the action of some environmental factors which alter host susceptibility and facilitate the development of RA, or it could be secondary to the particular, unknown biology of the β-thal population which predisposes towards diseases such as RA.

These findings have been confusing, and have led some authors to assume the existence of an 'arthritis of β-thal subjects' [10], which can be considered as a mild form of inflammatory arthritis affecting β-thal subjects.

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1. Montecucco C, Caporali R, Rossi S, Epis O. Rheumatoid arthritis in beta-thalassaemia trait. Br J Rheumatol 1999;38:1021–2.
2. Marcolongo R, Trotta F, Scaramelli M. Beta-thalassaemic trait and rheumatoid arthritis. Lancet 1975;i:1141.

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3. Baserga A. La biologia della 'popolazione' talassemica: interrogativi e prospettive di ricerche. Progresso Med 1972;28:413–6.
4. Gorriz L, De Leon C, Herrero-Beaumont G, Fernandez del Vallado P. Arthritis in beta-thalassemia minor. Arthritis Rheum 1983;26:1292–3.
5. Dovigo L, Sighinolfi L, Ogier C *et al.* Active and total T-cells in patients with rheumatoid arthritis and heterozygous b-thalassaemia. X European Cong Rheumatol 1983, June 26–July 2, Moscow (Abstract 932).
6. Ogier C, Sighinolfi L, Cervellati F *et al.* Circulating active T-cells in patients with rheumatoid arthritis and heterozygous beta-thalassemia. Rhumatologie 1985;15:85–8.
7. Dovigo L, Spisani S, Sighinolfi L *et al.* Rosette E attive totali e funzione dei PMN in pazienti con AR e b-talassemia minor. Arch Ortop Reumatol 1983;96:58(abstract).
8. Trotta F, Conighi C, Mattiuz PL *et al.* Antigeni HLA-DR nell'artrite reumatoide di pazienti portatori di beta-talassemia eterozigote. Reumatismo 1986;38(Suppl. 3):153.
9. Trotta F, Scaramelli M, Dovigo L *et al.* L'artrite reumatoide del beta-talassemico eterozigote. Reumatismo 1984;36:225–9.
10. Schlumpf U, Gerber N, Bunzli H *et al.* Arthritiden bei thalassaemia minor. Schweiz Med Wochenschr 1977;107:1156–2.

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Reply

We thank Drs Castellino *et al.* for their interest in our paper. These colleagues work in a district with a very high prevalence of β-thalassaemia (β-thal) and have great experience in this field. We are pleased to know that they agree with our conclusions.

As for the specific points raised in their letter, we are aware that the in-patients of a Department of General Medicine may not be representative of the whole population. Since a higher than expected frequency of β-thal trait in rheumatoid arthritis (RA) was reported by Marcolongo *et al.* [1], the main aim of our work has been to demonstrate that the prevalence of β-thal trait was higher in RA patients than in patients with other inflammatory rheumatic diseases. The frequency of β-thal in patients with connective tissue diseases and seronegative spondyloarthropathies was similar to that expected for the whole population according to their geographic distribution. Nevertheless, the unpublished observations by Castellino *et al.* suggesting that β-thal may be less frequent in systemic lupus erythematosus patients than in the general population should stimulate further research.

The studies reported by Castellino *et al.* on T lymphocytes and HLA antigens are interesting, but do not give any additional information about whether RA and β-thal are linked by genetic factors, by environmental factors or by both.

Finally, an important question is how 'rheumatoid' is RA in β-thal patients? In our study, the frequency of rheumatoid factor was similar in patients with and without β-thal. Castellino *et al.* state that the onset, course, joint involvement and clinical features do not significantly differ between the two groups; however β-thal patients show 'a reduction of systemic complications, in particular rheumatoid nodules' and 'a lower value of erythrocyte sedimentation rate (related to the severity of the disease)'. We are carrying out a comparative study on clinical, laboratory and radiographic features of RA associated with β-thal trait. Although our data are still preliminary we have found a trend for a lower frequency of rheumatoid nodules in β-thal patients while other extra-articular features, e.g. sicca symptoms, seem to occur more frequently. Some difference may be also observed between β-thal and non-β-thal patients for disease activity. However, in our opinion, ESR does not appear a useful surrogate marker in patients with β-thal trait because of microcytosis and polyglobulia.

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1. Marcolongo R, Trotta F, Scaramelli M. Beta-thalassaemic trait and rheumatoid arthritis. Lancet 1975;i:1141.