Relationship between Iron Status and Recrudescent Herpes Labialis

P.-J. Lamey*, P.A. Biagioni

A prospective study was undertaken to assess the relationship between recrudescent herpes labialis and host iron status. Forty-one patients with recrudescent herpes labialis, proven by herpes simplex virus isolation, were studied along with an equal number of age-and-sex matched control subjects. The iron status of patients and controls were assessed by haematine assay of ferritin. The iron (ferritin) level in patients with recrudescent herpes labialis was significantly ($p < 0.01$) lower than in the control group. Only one patient was anaemic. Sideropenia appears to be a common finding in patients with recrudescent herpes labialis. The relationship between sideropenia and recrudescent herpes labialis requires further study as it may have implications for the management of the disease.

Sideropenia, or latent iron deficiency, is defined as a condition marked by a deficiency of iron in the body. Iron is stored in tissue in two forms: as a soluble form, ferritin and as an unsoluble form, haemosiderin. About 70 % of stored iron is present as ferritin with the remainder as haemosiderin. In adults with a normal iron balance, plasma ferritin levels for men are in the range of 28–220 µg/l with a mean of 103 µg/l. For women the range is 30–185 µg/l with a mean of 70 µg/l. In sideropenic individuals, plasma ferritin levels of 5.3–32 µg/l are found in conjunction with normal haemoglobin levels (1).

Both human and animal studies have shown that inadequate levels of iron and other minerals such as zinc and copper may alter an individual's immunocompetence (2) by altering the effectiveness of the cell-mediated complement system, the bactericidal activity of phagocytes, and antibody secretion and affinity (3). Therefore the host's ability to withstand infection may be impaired by reduced levels of iron. The degree of impairment is still a controversial point as directly attributing a host's level of immunocompetence to micronutrient deficiencies is difficult. Other micro- and macro-nutrient deficiencies may well be present in vivo, and it may be the complex combination of deficiencies which is deleterious to host resistance.

To the best of our knowledge investigations of micro-nutrient deficiencies and infections have almost exclusively involved cases of bacterial infection (4–7), although the relationship has been studied in patients with HIV (8). Our investigation was directed at the iron levels within the body during recrudescent labial herpetic infection.

A number of trigger factors for recurrent episodes of infection are recognised, including stress, menstruation, trauma and sunlight. In immunocompromised individuals it is clear that host factors can facilitate or worsen herpes labialis lesions, but the situation is less clear in apparently healthy individuals susceptible to the disease. Thus the present study aimed to investigate the iron status of apparently otherwise healthy individuals who suffered from recurrent herpes labialis.

Materials and Methods. Forty-one patients were included in the study after answering an advertisement in a local newspaper. Of these 32 were females and 9 were males. Their ages ranged from 22 to 47 years with a mean of 32 years. All were in good health apart from their recrudescent herpes labialis lesions. No hospitalised patients were involved. An age-and-sex matched control group of healthy hospital staff who had no history of herpes labialis and were not receiving medication were also included in the study. Patients were asked to report when they first developed what they thought were herpes labialis lesions. Criteria for inclusion of patients in the study was the documented isolation of herpes simplex virus using a Hep 2 cell line. All patients and control subjects gave informed consent to participate in the study. Blood samples were collected by venipuncture for assay of haemoglobin, corrected whole-blood folate, vitamin B_{12}, ferritin levels and herpes simplex antibody titres. A nonparametric Mann-Whitney U-test was used to compare ferritin levels in patients and controls, and these results were confirmed by parametric analysis. A value of < 0.05 was considered statistically significant.

For the purposes of this study recurrence was defined as a subclinical infection, and recrudescence as an infection with clinical manifestations.

Department of Oral Medicine, Oral Surgery and Oral Pathology, School of Clinical Dentistry, Queen's University of Belfast, Royal Victoria Hospital, Grosvenor Road, Belfast, BT12 6BP, UK.

Results and Discussion. Positive virus culture was obtained in 39 of the 41 patients. In one case herpes simplex type 2 was isolated, and in all other cases herpes simplex type 1 was isolated. The two patients in whom the virus was not isolated had had their lesion for over 48 hours, whereas all other patients reported within 24 hours of onset of their lesion(s). Of these 41 patients only one patient was considered anaemic (haemoglobin 10.2 g/dl). This could not be directly explained, due to an inadequate history, but menorrhagia would appear the most likely cause. Normal haemoglobin values were found for the age-and-sex-matched control group (12–18 g/dl). Assays of corrected whole-blood folate fell within normal levels for all patients and controls. Two patients had borderline low vitamin B_{12} levels (158 and 166 pg/ml). Figure 1 illustrates the ferritin levels for patients (the majority of whom were within the sideropenia region of < 40 ng/ml) and control subjects. Herpes simplex antibody titres showed a great deal of variability ranging from 1:16 to 1: 64 within the patient group.

This study reveals that sideropenia frequently occurs in otherwise healthy patients who are suffering from recrudescent herpes labialis. Its prevalence among people experiencing an asymptomatic recurrence is not known. The significance of this finding is uncertain since, at least in relation to bacterial infections, there seem to be two schools of thought in the literature: one which suggests that iron deficiency predisposes an individual to infection and another which suggests that iron overload increases susceptibility to infection (9). Thus there is no consensus on the relationship between iron deficiency and resistance to infection. Certain effects of iron deficiency have been identified, namely that cellular immunity is frequently altered in man. Humoral immunity on the other hand is far less affected, and bactericidal activity is decreased. However, even when these abnormalities are identified in iron-deficient individuals, their exact clinical and biological relevance is still uncertain. With respect to herpetic infection, the relationship between resistance to infection and iron deficiency may be important in that reduced cellular immunity may induce what normally would be a recurrent asymptomatic reactivation of the latent virus to develop into a recrudescent reactivation. This may explain the disparity between the frequency in the population who have serum antibodies and the recrudescent reactivation frequency. Furthermore, one of the major epidemiological determinants for herpes simplex virus infection is socioeconomic level (10), and nutritional standards in lower economic groups may also play a role.

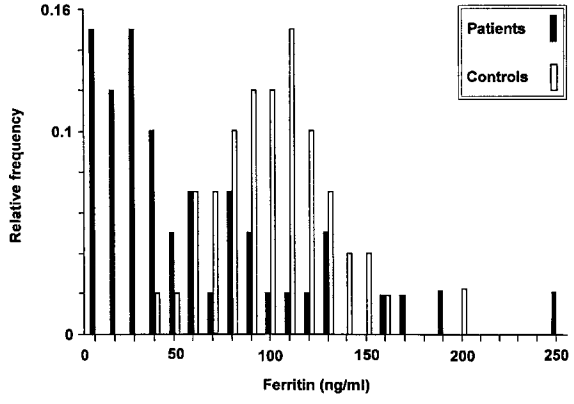

Figure 1: Relative frequency of ferritin levels in patients and control subjects.

In conclusion, a role of iron deficiency in recrudescent herpes labialis is confirmed. The results presented here demonstrate this association in a high percentage of individuals so that the exact role of iron deficiency in herpetic infection needs clarification especially with respect to asymptomatic recurrence.

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