Resistance to activated Protein C in Patients with Venous Leg Ulcers

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Key Words
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Resistance to activated protein C (APC) is the most frequent cause of inherited thrombophilia [1]. The Leiden Thrombophilia Study detected resistance to APC in 21% of 301 unselected consecutive patients with a first episode of objectively confirmed diagnosis of deep-vein thrombosis (DVT) [2]. Among a matched control group, the incidence of resistance to APC was 5%. This represents a 7-fold increase in the risk of DVT in persons with resistance to APC (odds ratio 6.6, 95% confidence interval 3.6- to 12-fold). In contrast, a study from the University Hospital of Geneva detected resistance to APC in only 5.5% of 146 unselected patients with pulmonary embolism, compared to 4.0% of patients with suspicion of pulmonary embolism, in whom the diagnosis could not be confirmed (statistically no difference, p < 0.66) [3]. The striking difference might be explained in part by patient selection. Since resistance to APC has practical consequences for the particular individual, it is necessary to identify subgroups of persons in whom systematic screening for resistance to APC would be justified.

Patients with venous leg ulcers might represent a subgroup with a high prevalence of resistance to APC. Munkvad and Jørgensen [4] reported resistance to APC to be prevalent in 26% of 47 consecutive patients with venous leg ulceration (95% confidence interval 14-41%). To date we could confirm resistance to APC in several patients with venous leg ulcers, especially in those with a positive family history for leg ulcers. Assuming that about two thirds of the patients with venous leg ulceration do have postthrombotic damage of their deep-veins and as a consequence postthrombotic syndrome [5], resistance to APC might be especially prevalent among patients with postthrombotic leg ulceration.

This led us to perform a pilot study and to examine 20 consecutive patients presenting for venous leg ulceration. The diagnosis of venous leg ulceration was based on clinical criteria and Doppler ultrasound examination [5]. At the time of blood sampling, none of the patients received heparin or oral anticoagulants. Six patients had a personal history of prior DVT. None of the patients had a family history of thrombophilia. Blood was collected in citrated glass tubes (sodium citrate, 0.11 mol/l), and plasma was prepared by centrifugation (3,000 g for 10 min) and stored at -80 °C. The APC sensitivity ratio was measured with the Coatest APC resistance kit (Cromogenix,
Mölndal, Sweden). Briefly, activated prothrombin time (APTT) is measured in the absence of APC and after APC has been added to the test plasma. The APC sensitivity ratio (APTT + APC/APTT) is considered abnormal if equal or below 2.0. Four of 20 consecutive patients with venous leg ulceration had resistance to APC (fig. 1). Two of those 4 patients had a positive personal history of DVT, compared to 4 of the other 16 patients without resistance to APC (no significant difference).

Fig. 1. Distribution of APC sensitivity ratio in patients with venous leg ulcers (n = 20).

This pilot study is limited by the small sample size and does not fulfill rigorous criteria, such as confirmation of factor V Leiden mutation by DNA analysis [6,7], nor did we include a control group. However, the result is in excellent accordance with the findings as reported by Munkvad and Jørgensen [4]. This underlines the interest of future studies to investigate the prevalence of postthrombotic pathologies and resistance to APC in patients with venous leg ulcers. Patients with postthrombotic leg ulcers and – in the case of a positive finding – their children might represent a group of persons in whom screening for resistance to APC is justified.

References

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Rejection of Punch Grafts in Three Cases of Herpes-simplex-induced Lip Leucoderma: Caution and Precaution
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Key Words
Leucoderma of the lip · Herpes simplex · Punch grafting

Lip leucoderma due to recurrent herpes labialis is not uncommon. Medical management hardly ever yields any satisfactory result [1]. Therefore, various surgical modalities [2] may be tried to correct such lesions. We herein describe our experience of treating herpes-simplex-induced lip leucoderma (HILL) by punch grafting.

A 19-year-old female presented with leucoderma of the lower lip due to recurrent herpes labialis. Medical treatment tried for 7 months failed to restore the colour of the lip. The case was taken up for autologous miniature punch grafting. Since the patch of leucoderma was very small, only one 2-mm graft was sufficient to cover the area. The procedure was undertaken with proper antiseptic and aseptic measures. The dressing was opened on the 3rd day. The graft was found to have taken well. Again a dressing was applied. On the 5th day, while the dressing was re-opened, 4-5 small vesicles were noted at the periphery of the graft and the graft was seen to be detached from its bed. It was put in its place again followed by dressing. On the 7th postoperative day, the graft was found to be totally separated from its bed. There were 4-5 small grouped vesicles with erythema at the base.

A graft usually takes within 48-96 h [3]. In our case, it had taken well as observed on the 3rd day. However, from the 5th day onwards it showed signs of rejection. This sequence of events interested us to find out whether it was merely coincidental or whether there was any cause-and-effect relationship between punch grafting and development of herpes labialis. To probe this further, 2 more patients with HILL were scheduled for punch grafting. In a 20-year-old male, 3 grafts were necessary for the patch and in the other subject, a 27-year-old male, 6 grafts were used to cover the leucodermic patch on the lower lip. Almost the same sequence of events followed in these 2 cases. On the 3rd or 4th day, the grafts were taken but from the 5th to 7th day onwards they showed signs of rejection following the appearance of multiple small vesicles at the grafted sites. To find out the cause of rejection of punch grafts, a thorough investigation into the pathomechanism of formation of herpes labialis is necessary. Two types of degeneration [4] of the epidermis occur in herpes simplex infection, i.e. ballooning degeneration and reticular degeneration. Ballooning degeneration causes marked swelling of the epidermal cells and loss of intercellular bridges leading to acantholysis. Since it causes dissolution of the lower epidermis, it takes part in the rejection of the graft. Reticular degeneration represents a process in which the epidermal cells become greatly distended by intracellular oedema, as a result of which many of the cell walls burst. Reticular degeneration occurs mainly at the periphery of the viral vesicles which might be further adding to the process of rejection of the graft by formation of perigraft vesicle(s). These degenerative processes disturb the graft not only at the bed but also all round the graft by breaking its attachment from the surrounding tissues. However, this was a matter of ‘caution’ to us while undertaking the procedure. We realized that as a ‘precaution’ one must establish the history of herpes labialis before using grafts to cover lip leucoderma. If there is a positive history, other methods or repigmentation should be resorted to rather than grafting. Whether prophylactic acyclovir for 6 months to 1 year prior to the punch grafting can help such cases is a matter of conjecture. Presently, a study of this possibility is in progress.
A 47-year-old Irish man presented with a 10-year history of marked pruritus involving the brachioradial areas of both forearms. It had a seasonal pattern with an onset each year in July and would persist throughout the summer but gradually fade and disappear between October and November only to recur the following year. The pruritus also demonstrated a diurnal variation, being much more intense during the evening and night, and would often disturb his sleep. Intense sunlight exposure and a rise in environmental temperature were felt to be exacerbating factors. Despite his intense pruritus, at no point had