Visualization of microcirculatory disorders in haemorrhagic fever with renal syndrome

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Haemorrhagic fever with renal syndrome (HFRS) is a severe virus-induced disease with renal involvement, first described in 1935 in the Far East of Russia. It is a zoonosis, with humans being affected by contact with animals (or their excretions) carrying the virus. While it was originally thought that the disease was unique to the Asian part of Russia, more recently epidemic outbreaks as well as sporadic cases of HFRS were also noted in Eastern Europe, Scandinavia, or even Western Europe [1,2]. The Hantavirus has by now been well characterized on a molecular level and it has become apparent that Hantavirus strains causing disease with more adverse prognosis prevail in the Far East of Russia, whereas strains causing more benign disease are found in Western Europe.

According to our experience, in the Far East of Russia the incidence varies from 18 to 60 per 100000 of population, with a mortality rate of 1-6.5% [3].

Clinically the disease is characterized by haemorrhagic lesions, circulatory disturbances, and renal involvement presenting as acute renal failure and characterized by interstitial nephritis. Vascular injury is the hallmark of pathomorphology. It appears as if the virus has a specific affinity to endothelial cells, i.e. endothelial tropism; the earliest, most characteristic and most severe lesions concern the vascular wall. Such lesions include oedema of the vessel wall, regressive lesions terminating in necrosis of the wall microvessels, i.e. arterioles, capillaries, and venules [4]. The functional counterparts are increased vascular permeability and haemorrhage. Vascular injury will ultimately lead to stasis and arteriolar or venular thrombosis [5].

These vascular changes are prominent in visceral organs, particularly the kidney, the pituitary and adrenal glands, the right atrium, and the central nervous system [6]. Their occurrence in the skin and conjunctiva as well opens a fascinating possibility to visualize the sequence of events leading to vascular necrosis and haemorrhage.

Starting in 1950, we have tried to document microcirculatory changes in Khabarovsk, a region endemic for HFRS, at the Khabarovsk Medical Institute. We studied a total of 120 patients using biomicroscopy with a specifically designed device and investigated (i) the nail-fold and (ii) the conjunctiva of the eyeball.

Here we wish to summarize some of the salient features.

The type and the intensity of microcirculatory changes depend on the stage of the disease. Most severe changes were found in the oligoanuric phase, less pronounced changes in the polyuric phase, and some minor abnormalities only during the phase of convalescence. During the oligoanuric phase, the arteriolar/venular calibre ratio was 1:4 to 1:5 and irregularities of the venular calibre were visible. This was accompanied by reduced numbers of functioning capillaries and capillary drop-out (no-flow capillaries). Accompanying changes included (conjunctival) oedema, sludge formation, i.e. erythrocyte aggregation in the vessels, leading to a slow-down of blood flow and thrombosis. This was noted in capillaries, venules, and arterioles. During the polyuric phase, microvascular abnormalities were less pronounced. In the conjunctiva numerous haemorrhages were noted, perivascular oedema tended to regress, as did the ratio arteriolar:venular diameter. Single vessels had a ‘ball-like’ appearance resulting from dilatation secondary to intravascular erythrocyte aggregation.

During the phase of reconvalescence further improvement of microcirculatory changes was noted, but occasionally intravascular aggregation of erythrocytes, dilatation of venules, irregular vascular calibre and capillary drop-out were still demonstrable. These abnormalities regressed slowly.

Typical findings are illustrated in Figures 1–3.

The question arises whether increased vascular permeability is susceptible to pharmacological intervention. We tried sodium-etamsylate in such patients (n = 10). In a double-blind study, sodium-etamsylate caused rapid normalization of increased vascular permeability and microcirculatory disorders as examined in the conjunctiva (Figures 4,5).

References

Fig. 1. Oliguric phase. Generalized aggregation of erythrocytes (sludge-phenomenon) in all vessels. Capillary closure.

Fig. 2. Polyuric phase. Venous congestion. Venous distension and tortuosity.

Fig. 3. Phase of convalescence. Microcirculation is being normalized. Some capillary sludge.

Fig. 4. The influence of sodium-etamsylate on conjunctival microcirculation in a patient with severe HFRS. Initial state (before therapy).

Fig. 5. After three injections (500 mg each): decrease of sludge.


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