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(SHORT COMMUNICATION)

Adrenocortical response in influenza as a pattern for using corticosteroids in COVID-19

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Abstract

In patients with influenza hospitalized during the epidemic (Moscow, 1977) blood levels of 11-oxycorticosteroids (11-OX) and tyrosine were determined. Due to specific features of tyrosine metabolism, its blood level is virtually determined by two factors: the functional competence of hepatocytes and tissue provision with glucocorticoids. Similar hypertyrosinemia was revealed in 11 patients with a severe complicated course of the disease and in 9 of 22 patients with a relatively light course of influenza. At virtually the same "intoxication start" the adrenocortical response was dramatically different in "severe" and "relatively light" patients: at the beginning of the disease in the "relatively light" patients there was a pronounced increase in the 11-OX level, whereas in the "severe" patients the level of 11-OX retained at the level normal for the physiological rest conditions. Thus, the clinical course of the acute infection was associated with the presence or absence of the well-timed adrenocortical response.

It seems that corticosteroid preparations would be most useful at the beginning of acute infection – as imitation of the full-value adrenocortical response. Possibly, the same would be useful for treatment of COVID-19.

Keywords: Adrenocortical response; Acute influenza; Corticosteroid therapy; Analogy with COVID-19

1. Introduction

Patients with severe course of COVID-19 infection are treated with various powerful modern pharmaceuticals, among which corticosteroid preparations are also used. However, corticosteroid preparations are fundamentally different from all other pharmaceuticals: they are analogs of natural adrenocortical hormones which play an important, if not the decisive, role under stress situations in humans and animals. Therefore, a reasonable question emerges: what can be the contribution of natural hormones to the course of COVID-19? What can be the best pattern of using corticosteroid preparations?

That is why I would like to reproduce the main results of the study initiated by Prof. R.M. Zaslavskaya and performed in February 1977 in Moscow during epidemic of influenza caused by the group A virus. This study was published in 1978 [1] and briefly reproduced in 2016 [2]. It seems that despite the small number of patients under study, the data can be of help for understanding the role of adrenocortical response in the course of an acute viral infection and may be a remark to the discussion about the use of corticosteroids in patients with COVID-19.

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2. Material and methods

Thirty-three patients with influenza hospitalized because of severe conditions were under study. Blood samples were taken on empty stomach on the next morning (usually it was the 2^{d}–4th day from the onset of the disease) and then on the 7th–8th, 13th–14th, and 20th–21st days of the disease. In these samples the levels of 11-oxycorticosteroids (11-OX) and tyrosine were determined.

The level of 11-OX characterized the general activity of adrenal cortex. Blood tyrosine is not a routine laboratory parameter, but based on the specific features of this amino acid metabolism [3] its blood level may be assumed to be determined by activity of the hepatic enzyme tyrosine aminotransferase (TAT, EC 2.6.1.5). In its turn, the TAT activity depends on two factors: 1) Ability of the hepatocytes to synthesize the sufficient amount of the enzyme, i.e. on the *functional competence* of the liver, and 2) The entrance of corticosteroids into the liver, since TAT synthesis also depends on the glucocorticoid provision of the tissues [2]. Tyrosine was measured according to the work [4]. Thus, our "working hypothesis" was that blood tyrosine level was determined by the functional competence of the liver and corticosteroid provision of the body.

The data were processed after the patients left the hospital. According to the clinical course of influenza, the patients were subdivided into two groups: 11 patients (15-69 years old) with a long-term severe complicated course of the disease (pneumonia in 9, including bilateral in 6 patients, acute tracheobronchitis and severe tonsillitis in 2 patients) (the 1st group) and 22 patients (16-70 years old) with a relatively light course of the disease. The 1st group patients were in the hospital from 15 to 55 days (26.5 days, on average), the 2nd group patients – from 5 to 16 days (10.1 days, on average).

3. Results and discussion

In the 1st group blood tyrosine level was significantly increased in all patients in 22 of 40 samples during the hospitalization, being on average 102.5 ± 19.4 μg/ml at the first determination. Blood tyrosine level in healthy humans was 16.2 ± 0.9 μg/ml [2]. When processing the data for the 2nd group, the patients were distinguished with blood tyrosine level above 53 μg/ml at least in one sample. This conventional threshold value corresponded the doubled upper limit of the normal value (16.2 + 3σ) × 2 = 53 μg/ml. In the patients of the 2nd group values above this conventional threshold were recorded in 9 patients (90.2 ± 11.4 μg/ml on average) only at the first determination. These 9 patients' age was from 16 to 70, in 5 of them there were no complications, in 1 was local pneumonia and in 3 – acute tracheobronchitis.

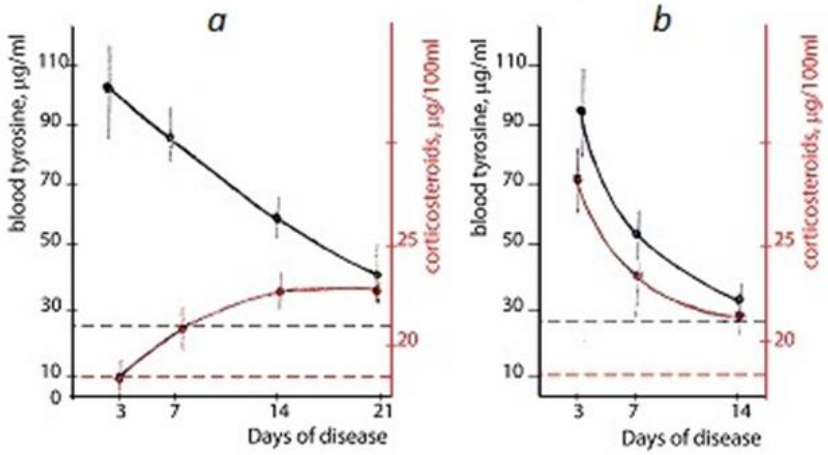

Figure 1 Changes in blood levels of tyrosine (black curves) and of 11-oxycorticosteroids (red curves) in patients with influenza. Interrupted lines indicate upper normal limits of tyrosine (black) and corticosteroids (red) under conditions of rest. a) Patients with a severe complicated course of the disease (the 1st group); b) Patients with a relatively light course of the disease (the 2^{int} group) (after [2]).

We assumed that such very high values of blood tyrosine should be a result not only of a probable hormonal insufficiency, but also of the liver intoxication. Thus, we assumed that 11 patients with the severe course of influenza and these 9 patients of the 2nd group with a relatively light course of the disease had virtually the same "intoxication start" (we denoted them as 2int – intoxicated). Behaviors of blood tyrosine and 11-oxycorticosteroids in the patients of the 1st and 2int groups are presented in the Figure. Blood tyrosine level decreased during the course of the disease in the patients of both groups, but in the 2int group patients this decrease was much faster (Figure).

However, the behavior of 11-oxycorticosteroids, i.e. the adrenocortical response of the patients of these two groups, during the disease occurred to be extremely interesting – it was dramatically different in the patients from the different groups. In 11 "severe" patients the level of hormones by the moment of hospitalization (i.e. usually by the 3-4 day of the disease) was in normal limits (for conditions of the rest!). In 9 patients of the 2nd group (2int) patients the level of hormones at the first measurement was significantly increased and remained elevated during the acute period of the disease.

Thus, at the severe course of influenza there was no increase in the synthesis of corticosteroid hormones, *i.e. the normal adrenocortical response was absent*; but the delayed activity of the adrenal cortex could promote secondary infections in this group, as it was really observed. (**Note**! In one patient of the 1st (severe!) group the arterial pressure at the entrance on the 2nd day of the disease was 85/60, she was injected intravenously with urbason (60 mg), she has the local pneumonia, hospitalization for 15 days).

The relatively light course of influenza in the 2int group patients was associated with *a pronounced and well-timed response of the adrenal cortex* at the beginning of the disease. Thus, it seems that the best solution would be to give corticosteroid preparations to patients with acute severe influenza as early as possible – *to imitate the natural well-timed adrenocortical response*, i.e. during the first 2-3 days of the disease.

4. Conclusion

It is reasonably to think that the organism's response to acute viral infection – now the World deals with COVID-19 – has to be fundamentally similar. In this case, the problem of using corticosteroids in the current pandemic should follow the natural pattern observed by us in acute influenza – corticosteroids should be given early, not waiting severe conditions.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There was no conflict of interests.

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Author's short biography

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Born 1934 in Moscow. Graduated Moscow State University, Faculty of Biology. From 1968 research interests: corticosteroids, role in organism and use in medicine. I have shown that blood tyrosine is index of metabolic action of CS and is promising as a laboratory parameter. From 2002 2007 retreated. Ph.D, Dr.Sci (Biology).