Neuroendocrinology Letters 2001; **22**:330–331
pii: NEL220501L01

Letter to the Editor

Clinical Study *by* **Ruediger Lorenz** *Received August 11, 2001*

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Sir – there are a lot of data that epileptic seizures may modify cytokine secretion in patients suffering from epilepsy and in experimental animals. In epileptic patients the secretion of IL 1α, IL1β and IL 6 in peripheral blood mononuclear cells was found to be enhanced [1]; in experimental animals after induction of seizures enhanced concentrations of IL 1β [2] and TNFα [3] inside the CNS were found. The findings in animals can be interpreted as adaptive, neuro-protective and seizure limiting phenomena [3, 4, 5]. But, very high concentrations of IL 1β can elicit epileptic activity by inhibition of inhibitory neurons [4].

For this reason the serum concentrations of cytokines in 41 epileptic patients in my pediatric office were determined. In 40 patients IL 1, in 24 IL 1α and IL 1β fractions, in 40 IL 6, and in 35 TNFα were determined. The mean age of the patients was 11 1/12 years (0 2/12 – 35 8/12 years), 32 were males, 9 females. Patients with signs of infection and patients, who had undergone neurosurgical treatment, were excluded.

The findings were as follows:

1. In 15 of 24 patients IL 1α and IL1β concentrations were enhanced (normal ranges as defined by 95% of population: < 4.0 pg/ml) ($p < 0.001$).
2. Concerning IL 1 (normal ranges: < 15 pg/ml), IL 1α and IL 1β differences between leftfocal and rightfocal epilepsies were found: the median of the concentrations in 12 leftfocal epilepsies was higher than in 9 rightfocal ones (IL 1:15.80 pg/ml vs. 8.85 pg/ml, IL 1α: 8.40 pg/ml vs. 3.30 pg/ml, IL 1β: 8.00 pg/ml vs. 3.80 pg/ml). Concerning IL 1α this difference was statistically significant ($p = 0.024$). The medians of the concentrations in 7 generalized and 6 multifocal epilepsies were between those of leftfocal and rightfocal ones with higher concentrations in generalized than in multifocal epilepsies. 7 epilepsies could not be classified exactly.
3. The medians of the concentrations of IL 6 in the examined patients were not elevated (normal range: ≤8,5 pg/ml).
4. A statistical analysis of the TNFα results was not possible because the laboratory's methods were changed, while the study was performed. So 2 subgroups existed with different normal ranges (< 20 pg/ml resp. < 12 pg/ml). These groups were too small for statistical evaluation. But it should be emphasized, that in leftfocal more than in rightfocal epilepsies elevations of the TNFα concentrations were found.

(Methods: Determination of IL1 by means of co-stimulationsassay, IL 1α: Elisa, IL 1β, IL 6, TNFα: Chemiluminescenceassay. Focus localization was determined by one or more of the following criteria: morphology of seizures, EEG, NMR, sonography, PET.)

There seems to be no influence of the following factors on serum cytokine concentrations: presence or absence of grand mal seizures, medication, distance between the point of time of taking the blood sample and the last seizure before it and the intrahemispheric localization of the focus.

Because of the small number of cases presented in my study I am interested if specialized hospitals could confirm my findings in a larger study. As other authors have found an influence of intra-hemispheric focus localization on immunological parameters [6], in this concern further investigations are necessary. It is an important question, too, if hemispheric dominance must be considered.

At this point of time my data give hints, that IL 1α and IL1β could be markers of epilepsy, which may help to discriminate paroxysmal events of epileptical and not epileptical origin.

The differences between leftfocal and rightfocal epilepsies confirm the results of an experimental study in mice, providing evidence of a suppression of lymphocyte function after leftsided cortexablation [7] and of a neurosurgical study in epileptic patients proving the same phenomenon in dominant hemispheric resection [8]. These findings and my data confirm themselves, because cortex ablation and cortex stimulation by epileptic activity may lead to opposite immunological effects.

If the differences in concentrations of cytokines in left- and rightfocal epilepsies are due to different amount of secretion induced by epileptic activity in the different hemispheres, which leads to greater or lower efflux of cytokines via the brain-blood-barrier or due to different stimulation of the peripheral immune system via the sympathic nerve or the neuroendocrine system, is another interesting question. So far as I know animal studies comparing cytokine secretion inside the CNS after left- and right (or dominant- and non dominant) hemispheric induction of seizures have not been performed. But the fact, that seizures induced in the right hemisphere effect cytokine secretion inside the CNS, has been proved [3]. A hint to the hypothesis of peripheral stimulation could be the findings in epileptic patients [1] and the neuroanatomical finding, that in some non-mammals habenula, which is an important nucleus in the neuroendocrine system, it is more extended in the left hemisphere than in the right one. But in this concern data in men are not available [9].

In my opinion cytokine secretions inside and outside the CNS are not independent phenomena. As it is well established, that melatonin has an influence on cytokine secretion [10] and that there is an anatomical connection between the corpus pineale and the habenula [9], we should take the role of melatonin as a regulator of cytokine secretion into consideration. Further investigations should deal with the intraindividual variations of cytokine secretion in epileptic patients during the light and the dark periods of the year. Seasonal variations of the frequency of seizures may be due to immunological changes induced by melatonin.

I hope, that my findings, questions and speculations lead to further investigations.

Acknowledgments

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