

Letter to the Editor

Cytokines and Epilepsy. A Clinical Study

Ruediger Lorenz

Brunnenstraße 54

D-34537 Bad Wildungen, Germany.

Received: January 19, 2002

Sir – In this letter I want to comment on my previous communication about cytokines and epilepsy [1]. Though in parts this commentary may be of anecdotal character, I hope, it will be ‘synthetic research’ as defined in this journal [2].

Cytokines developed in early evolutionary times. So, they interact in a similar manner in various species whose evolutionary pathways separated for some 500, 000, 000 years, for example, like in *mytilus edulis* and in humans [3].

The CNS regulates cytokine secretion and cytokines act on the CNS.

Statistical analysis of my data is not possible, but I have hints that the hemispheric differences of regulation [1] are due to dominant/non-dominant – and not to left/right hemisphere. I have no hints that they reflect a dominant hemisphere’s requirement of a special immunological protection, but I am sure, that the immune and endocrine system is regulated by the CNS in an antagonistic but manifold interacting way.

Therefore, considering the dominant hemisphere’s cortex as stimulating the immune and endocrine system is not of proper exactness. Interhemispheric connections [4] must be taken into account. By the way, these interactions do not only relate to regulation of the cytokine secretion in general, for it has been found that cytokine secretion inside the CNS reciprocates, too (I am sure that it is problematic to do a hard cut in this concern!): Limbic status epilepticus in the rat, induced by unilateral injection of kainat, leads to enhanced TNF α secretion in the other hemisphere, too [5]. Moreover, it is of importance as to which function of the immune and endocrine system is observed. The influence of the subcortical structures [6] has to be analysed, and, in addition to that intrahemispheric differentiation must be given attention: the anterior prefrontal region is of high importance in immunological concern [4]. There are hints in my patients, too, that especially *rostral foci* are combined with elevations of cytokines in the sera.

The case history of a girl presenting marked left sided frontotemporal cortical dysplasia with bizarre neurons and balloon cells (histology by Prof. Lahl, Bethel, Germany) and severe epilepsy gives hints for the importance of *rostral* CNS regions in immunological concern. Before frontotemporal resection combined with subpial dissections (Dr. Pannek, Bethel) was performed, despite many seizures no elevations of IL1-concentrations in the serum were found. After neurosurgical treatment, the girl not only did not present seizures, but there also was substantial progress concerning development of language and motoric faculties, demonstrating, that the dysplastic structures, besides epileptic stimulation, had effected inhibition. In accord with this, IL1-concentrations now were elevated. These findings may support the hypothesis, that in this case of severely altered CNS, there is an impairment of the immune system’s stimulation by the left *rostral* hemisphere.

The hypothesis that the left and right hemispheres influence the immune and endocrine system in different ways is supported by the observation that women with left temporal epilepsies have a tendency to have polycystic ovaries (the pathogenesis of which are excessive secretions of luteinizing hormone with higher pulse rates than normal), whereas woman with right temporal epilepsy have a tendency to hypogonadotropic hypogonadism. The influence of the intrahemispheric localization of the focus is demonstrated by the fact that in women with non-temporal rightsided foci, polycystic ovaries are also found [7].

There are hints, that melatonin participates in the network of cytokine secretion. In a boy suffering from intractable grand mal epilepsy the frequency of seizures in winter times was higher than in the summers, which condition could be observed during some years. It is known that some epileptic patients benefit from therapy with visible light [8]. Light influences secretion of melatonin and melatonin influences the immune system. I hypothesize, that these facts partly explain the observations.

Indeed, propranolol medication did not only lower excretion of 6-sulfamethoxy-melatonin in the patient's urine (Dr. Olcese, Hamburg) but also the concentrations of IL1 α and IL1 β in the serum. When propranolol was given, they amounted to 4.3 pg/ml resp. 3.9 pg/ml, whereas the mean concentrations (5 samples were examined), when propranolol was not given, amounted to 6.7 pg/ml resp. 5.8 pg/ml. But, unfortunately, an improvement of epilepsy was not seen when cytokines were suppressed. The author's IL1 α - and IL1 β -concentrations amounted to 5.8 pg/ml resp. 4.9 pg/ml, when 3 mg melatonin were given, and to 3.8 pg/ml resp. 3.1 pg/ml, when 10 mg propranolol were given (drugs were taken in the evening and blood samples were taken in the morning of the next day). In contradiction to these findings, in an erethic child suffering from epilepsy and tuberous sclerosis no differences between the IL1 α - and IL1 β -concentrations before and after beginning the melatonin treatment (6 mg in the evening) were seen. Melatonin plays an important role in the regulation of cytokine secretion. But the network of this regulation is a very complex one with many interconnecting pathways. The rhythmicity of the system augments this complexity in a dramatic manner [3].

Naturally, it is an important question, if therapeutic consequences can be derived from these findings. Cytokines have contrary effects: they destroy and repair [9], they can cause synaptic inhibition and excitation by inhibition of inhibition [10], and so it is difficult, to derive therapeutic concepts, which are based on influencing cytokines. But, cytokines are a very important part of epileptogenesis as is demonstrated by the following finding: whether patients with temporal lobe epilepsy will develop a sclerosis of the hippocampus can be dependent of the presence of certain IL1 β -polymorphisms [11]. However, other authors could not confirm these results [12].

An example demonstrating that the modification of cytokines could serve as a therapeutic principle in the treatment of epilepsy, is the following: Mice preinjected with preparations of shigella dysenteriae, which induce TNF α - and IL1 β production, presented more seizures after application of pentylenetetrazole than mice preinjected with saline. If TNF α - and IL1 β -antibodies were applied in the first group additionally, the induction of seizures was diminished [13].

Another way could be to influence melatonin itself. I have hints for my hypothesis, that vagus nerve stimulation acts partly via melatonin.

Finishing this commentary, I want to focus on a special condition: coinciding of epileptic seizures and psychotic symptoms, which can be expression of epilepsy or psychosis. Literature gives suggestion for the relevance of IL2 in psychosis: a treatment with IL2 is able to provoke symptoms of delusion, perturbances of cognition, and, to a lesser degree, of affects. The diminished production of IL2 induced by *in vitro* stimulating the lymphocytes of patients suffering from schizophrenia is interpreted as a reaction of exhaustion. Concentrations of IL2 in the cerebrospinal fluids of untreated schizophrenic patients are higher than those of controls (literature: see 14).

A 15 years old boy, whose (presumable monozygotic) twin a few months ago had suffered from a psychotic episode coinciding with an epileptic seizure, presented symptoms of excitation, anxiety, uttered the suspicion, that someone would have put something 'strange' in his beverage, and his sensation of his own body was changed. Some days later, he suffered from a grand mal seizure, and, despite treatment with valproate, 5 weeks later from a second one.

The cytokine findings in the sera were the following:

	IL1 (pg/ml)	IL1 α (pg/ml)	IL1 β (pg/ml)	IL2 (U/ml)	IL6 (pg/ml)
4 days after first seizure	14.1	6.9	7.0	7.40	14,8
3 months later	10.6	5.8	4.7	1.26	not defined

Laboratory, methods and normal values are mentioned in [1]. IL2 has been determined in the laboratory of Prof. K. P. Ringel, Aachen, by the means of enzymeimmunoassay.

Normal values: 0.5 U/ml – 2.5 U/ml.

Normal values of IL2 coincided with diminished psychotic symptoms. As values of IL1 α and IL1 β furthermore were elevated, when IL2 was in normal ranges, it seems likely, that the patient suffered from epilepsy and psychosis as different entities.

In a 14 years old boy suffering from epilepsy *ictual aphasia*, EEG- and NMR-findings suggested left temporal focus. He reported the feeling to be influenced ("like television without antenna") and of *déjà vue* and of *jamais vue*. The serum-concentrations of IL1 and IL6 were elevated, whereas IL2 was in normal ranges. This patient suffered from psychic aura of epileptic origin, as known in foci situated in the basal temporal region of language-dominant hemisphere [15].

So: determinations of cytokines can help to differentiate psychotic symptoms of epileptic and not epileptic origin.

Conclusions

1. Cytokines are a very interesting field of theoretical psychoneuroimmunological research.
2. Analysis of cytokines can be helpful in the treatment of epileptic patients.
3. In the future, perhaps treatment of epileptic patients based on modification of cytokines will be possible.

Acknowledgment. I am much obliged to Dr. Dagmar Dralle, who has introduced me in the field of neuropediatrics, Prof. Dr. Klaus-Peter Ringel because of many discussions concerning immunological questions, Karin Wagener because of very patient writing of my reports.

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