# Encephalomyelitis and Bornavirus – 100 years of research

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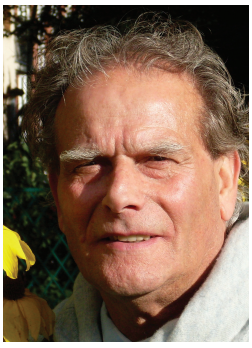

In 1911 Joest & Degen recognized that an encephalomyelitis non-purulenta, an inflammatory reaction localising in central areas of the brain of fatally diseased horses, was characteristic for a head disease, a so called "hitzige Kopfkrankheit", later on coined "Borna´sche Krankheit", Borna Disease.

Mammalians more often show silent infections than overt disease. Endemic infections in the indigenous host (the horse) of 60% in Europe, contrasted a low infection rate (< 1%) in Australia, whereas 30% of humans are infected (Germany, Australia).

Deadly infections, only seen in animals, suggest to have exacerbated the accumulation of viral antigen beyond critical thresholds, as deduced from successful antiviral therapy with amantadine. However, once this point of uncontrolled viral replication in the brain is reached, animals cannot survive.

Deduced from animal experiments infectious viral structures enter neuronal circuits and by axonal flow spread to the hippocampus and other limbic areas. Neurons of the dentate gyrus are most sensitive to degeneration. A typical laminar accumulation of antigen in hippocampal layers expressed in an intimate affinity to Kainat-1(KA-1) receptors, can be explained by affinity to the glutamatergic system. This parallels a high prevalence of p40 and p24 proteins in the retina, where glutamate receptors accumulate. Centrifugal spreading into the autonomic nerve system may influence the gastrotransmitter balance. Under natural conditions this accounts for colic symptoms (known in horses), possibly being also involved in the "Irritable Bowl Syndrome" of human Chronic Fatique Syndrome (CFS)-patients.

Neither infected tree shrews with altered social behaviour, nor BDV infected cats showed overt disease, although a severe encephalomyelitis lymphocytaria was found in limbic brain areas.

BDV-induced pathology becomes further complicated by the fact, that virus is present in brain and periphery, coinciding with severe neurological and psychiatric symptoms in vulnerable subjects.

The N- and P-proteins of BDV, produced abundantly, are shed into the blood plasma. They represent the major immunogenic components and are enriched in neurons and glial cells of the limbic system, most probably being responsible for changed functions in such cells and the consecutive neurotransmitter disturbances. A selective binding of viral proteins to brain structures functionally summarized as the limbic system parallels highest virus-, antigen-, and RNA loads in natural and experimental infections.

A double sandwich ELISA with coupled N- and P-protein-specific monoclonal antibodies measuring native viral proteins in blood, CSF or organs, as low as 1.5-3.0 ng/ml, allowed to catch circulating immune complexes (CICs), and by this opened new fields for epidemiological studies.

Humans seem to better control natural infections than animals, and the psychiatric symptoms coinciding with an activated viral state are most variable. Fatal outcomes have not been observed in humans, and BDV infection with encephalitis, as recently reported in China, is rare, but fits present concepts.

Viral footprints, like proteins and occasionally RNA are found in blood plasma, although the excreting cells remain unknown till now, but can be assumed to be present in spleen, liver, and bone marrow.

Approximately 5% of the population (16% of the infected individuals), diagnosed with affective disorders, suffers from frequent or chronic activation processes (based on antigen & CIC measurements) and/or presents with severe antigenemia in acute episodes. BDV infections in man are known globally (AU, AT, BR, FR, CZ, DE, IT, JP, GB, US, PL, CH, recently in LI, CN, and IR).

Regarding a selectivity of BDV components to mammalian limbic system structures, most probably to the KA-1 receptor of the glutamate system is supportive for the glutamate-deficiency hypothesis which points to depression and cognitive deficits. From this BDV should be considered a major cofactor in multi-factorial human psychiatric disorders. Non-specific stress events may initiate immune suppression causally leading to virus activation. Viral interference with the hypothalamic-pituitary gland (HPA)-axis influences such disease patterns to worsen and eventually to run into a chronic course.

To conclude, the concept of encephalomyelitis with peripheral lymphocytic infiltrations in the brain originally reported by Joest, seems not to be the cause of disease, although it was favoured for almost 100 years. Distinct behaviour and cognitive changes depending upon virus-induced disturbancies in the function of neuro- and gastrotransmitter networks are more likely to play a major etiopathogenetic role.

After clarification most of the biological parameters and evaluating a variety of infection models, BDV has attracted major interest and gained significant importance in human infections. Starting with antibody findings in psychiatric patients, followed by detection of antigen and immune complexes in blood of patients, controls and blood donors by Bode and her group (confirmed in Australia), the effective treatment with amantadine of patients carrying virus markers, offers new hope for major mood disorder patients (this therapy has also successfully been applied in diseased animals).

The recent ground breaking discovery of the N-gen of BDV integrated into the germ line (the so called EBLNs) with its possible influence on disease in humans provoke DNA analyses from mood disorder patients collected in Bode´s Biobank of 30.000 blood samples to lift the secret of a 40 million old gene on the balance of human mood and health.

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