

## ARE *CHLAMYDOPHILA* INFECTIONS A MAJOR FACTOR IN NEUROLOGIC AND PSYCHIATRIC DISEASES?

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**Background:** The cause of neurologic symptoms is obvious, if acute inflammatory processes occur in the central nervous system or in the surrounding tissue, for example by *Neisseria meningitis*, *Herpes simplex* or other pathogens. In contrast, chronic diseases without an identified pathogen present an important problem in neurology and in medicine. A pathogen may be recognized in the beginning of a disease, but symptoms may disappear after short time. After months or years the patient will not remember the infectious episode, furthermore, the symptoms of the relapsing disease may be now very different. PCR-techniques document, that despite resolution of symptoms a pathogen can reside inside the body for years. *Chlamydomphila*, especially *C. pneumoniae* and *C. psittaci* appear as a major representative of these intracellular bacteria in neurologic and psychiatric diseases because of their neurotropism. Monocytes infected with *C. pneumoniae* and *C. psittaci* can pass the blood brain barrier (BBB) and infect glial, microglial and neuronal cells.

### Life cycle of *Chlamydomphila*

*Chlamydomphila* are obligate intracellular bacterial pathogens, which survive by their entry into cells. The life cycle of *Chlamydomphila* begins with attachment to the cell by infectious elementary bodies (EB), which can transform after fusion with phagosomes to non-infectious reticulate bodies (RB). RBs are the longterm survivors but can reorganize into the infectious EBs. *Chlamydomphila* are the only bacteria, which can induce and inhibit cell apoptosis. In monocytes and other mononuclear cells they can stimulate production of inflammatory cytokines.

### Diseases Associated with *Chlamydomphila* Infections

*C.pneumoniae* is common in human and was discovered as cause of respiratory illness, *C.psittaci* as cause of pneumonia and as ornithosis. *C.pneumoniae* seems to initiate atheromas and the progression to arteriosclerosis, causing cardiovascular and cerebrovascular diseases. Compared to healthy controls, significantly more frequent persistent infections with *Chlamydomphila* have been found in Alzheimer patients, Multiple Sclerosis patients, schizophrenia and autism disorders.

### Variants of HLA genes were found associated with neurologic and psychiatric disorders

Immune response genes of the polymorphic HLA system are responsible for the elimination of infectious microorganisms. Certain HLA variants were found in many association studies to occur more frequently in multiple sclerosis, narcolepsy, schizophrenia and other neurologic and psychiatric diseases. The analysis by Shi et al. in Nature 2009 concluded that the region of immune response genes, located on chromosome 6p21.3-22.1 shows a stronger association with schizophrenia than all other genetic factors together<sup>1</sup>.

### Immune cells evolved from nerve cells, MHC/HLA class I genes regulate CNS synapses

Many structures, which were thought to be structures of the immune system like the T cell receptor, the peptide transporter system TAP and MHC/HLA class I genes are also expressed in the CNS. A completely new understanding of the function of MHC genes in the CNS has been discovered by Carla Shatz and her group, showing that MHC class I genes regulate CNS synapses<sup>2</sup>.

### Arising questions

1. Are chronic infections with *Chlamydomphila* in neurologic diseases and in schizophrenia located in the blood and/or the brain?
2. Could failure of proper cellular processing and/or transport and/or presentation of immunogenic antigens from infectious organisms result in incompetent responses against *Chlamydomphila*?
3. Do neuronal or glial cells in the brain have to be infected with *Chlamydomphila* to disturb neuronal functions?

### Some of our findings and answers

#### 1. Persistent *Chlamydomphila* infections in schizophrenia

- We found 40% of 72 schizophrenic German Caucasian patients positive for *C. pneumoniae* and *C. psittaci* (6% of 225 control individuals,  $p=1.39 \times 10^9$ ), identified with RT-PCR in blood samples<sup>3</sup>. In **blinded** post mortem brain samples of American Caucasian individuals, 5,7% of the controls (N=35) and 23.53% of schizophrenic patients (N=34) were positive for *Chlamydomphila* ( $p=0.045$ ). Brain samples of schizophrenic patients were 4 x more often infected with *Chlamydomphila* than controls, samples of bipolar patients (N=32) 3 x more often<sup>4</sup>.

#### 2. Immune gene variants of the HLA system predisposing to schizophrenia

We found that individuals with HLA-A10 gene variants and a persistent *Chlamydomphila* infection had a fifty-fold increased relative risk of developing schizophrenia, compared to uninfected individuals ( $p=8.03 \times 10^5$ ). Other immune gene variants responsible for transportation (TAP) and loading of peptides (Tapasin) onto HLA molecules

were additional risk factors. The transporting-loading proteins and the HLA class I surface molecules apparently do not present immunogenic *Chlamydomophila* peptides.

**3. An altered detrimental response to interferons in schizophrenia**

In schizophrenic patients with persistent *Chlamydomophila* infections and carriers of HLA-A10 and an HLA-J variant we found a paradoxical response to interferons causing downregulation of the HLA-A10 expression preventing immune responses (unpublished results).

**4. Benefit of Adoptive Cell Therapy (ACT) in neurologic and psychiatric diseases**

Ten patients with psychiatric disorders (schizophrenia N=5, depression N=4, autism N=1) received ACT as adjuvant therapy once weekly for several months. The most prominent result was the recovery of energy and of social competence.

Two patients with relapsing multiple sclerosis receive ACT since years (the female patient, age 37y, since 13y, 6 relapses; the male patient, age 38y, since 3y, no relapse). Both patients continue working. Clear benefits were also observed in a female patient with Parkinson disease (age 82y), in a patient with restless legs (age 75y) and one patient with Alzheimer Disease (age 81y).

**Conclusions**

The association of immune response gene (HLA) variants with neurologic and psychiatric diseases suggests the involvement of microbial pathogens in these diseases. In Alzheimer disease, multiple sclerosis, schizophrenia and cerebrovascular arteriosclerosis *Chlamydomophila* have been identified in the majority of patients. The success of ACT may come from attacks against microbial pathogens and the secretion of neurotrophins by activated immune cells

- 1) Shi et al. Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature* 2009;460:753-7
- 2) Goddard CA, Butts DA, Schatz CJ. Regulation of CNS synapses by neuronal MHC class I. *Proc Natl Acad Sci USA* 2007;104:6828-33
- 3) Fellerhoff B, Laumbacher B, Mueller N, Gu S, Wank R. Association between *Chlamydomophila* infections, schizophrenia and risk of HLA-A10. *Mol Psychiatry* 2007; 12:264-72
- 4) Fellerhoff B, Wank R. Increased prevalence of *Chlamydomophila* DNA in post-mortem brain frontal cortex from patients with schizophrenia. *Schiz. Research* 2011; 129:191-195