Mild Encephalitis Underlying Psychiatric Disorder - A Reconsideration and Hypothesis exemplified on Borna Disease

K. Bechter

Dept. Psychotherapeutic Medicine and Psychosomatics (head PD Dr. K. Bechter) of Dept. Psychiatry II, University of Ulm (head Prof. Dr. R. Schöttler), Bezirkskrankenhaus Günzburg (Germany)

Summary

Earlier findings suggested mild Borna disease virus encephalitis (BDV ME) possibly underlying some schizophrenic or affective disorders. Here the hypothesis of mild encephalitis (ME) is considered generally. ME from viral, retroviral or immune origin within a multicausal especially immuno-genetic framework could underlie psychiatric disorders. A preliminary ME working definition is proposed and ME hypothesis considered on: a) Known (meningo-) encephalitis with and without neurological symptoms, b) Schizophrenia (assumed to represent core psychopathological syndrome from mild brain pathology), c) Diagnostic methods and respective limitations. d) BDV infection. - It is found, that ME can explain: 1. A spectrum of psychiatric disorders of unknown etiology. 2. Crucial findings and symptoms in schizophrenia: slight brain atrophy over time but temporary volume increases, explainable as degeneration overall but sometimes mild swelling from inflammation; disturbed brain metabolism and function; variable disease courses; general epidemiology, especially age-related variation of disease onset as from newly acquired viral (or retroviral) infections (pathogenicity of viral infections known varying with age from developmental host factors); post-mortem and in-vivo findings compatible with mild inflammation and immune activation; genetic liability factors, as known in many, especially viral, infections. 3. Low sensitivity of available diagnostic methods.

Introduction

Borna disease virus (BDV) was recently recognized as a possible cause of psychiatric disorders [reviews: 13, 17, 18, 26, 62, 76, 86, 179]. When discussing our hypothesis of mild BDV encephalitis, as a major problem evolved definition respectively diagnostic criteria of encephalitis causing psychiatric disorders. A reconsideration of encephalitis definition and possible implications from a psychiatric clinicians point of view is attempted here. Encephalitis is widely neglected in present psychiatry, the term not appearing at all in the majority of psychiatric textbooks or just with historical remarks, preferably on v. Economo encephalitis. Definition of 'encephalitis' and 'inflammation' is differing between various scientific and clinical disciplines (though unrecognized frequently), apparently dependent from methodological issues inherent to the various approaches themselves and limitations of respective technical methods used. For example, clinical neurology established diagnostic

Key Words: Mild encephalitis - schizophrenia - affective psychosis - Borna disease virus - brain atrophy - cerebrospinal fluid - immunopathology.
methods, but suffers from an ascertainment bias of mild cases from various reasons [9]. Neurology as a discipline apparently does not deal with patients suffering exclusively from psychiatric symptoms but lacking neurological deficits, the group of patients dealt with here. Virology usually defines “inflammation” with detection of cellular infiltrates under the microscope, although chemokines and cytokine expression or neurotransmitter alterations and other poorly investigated humoral alterations may precede cellular infiltration [compare for example 58, 187]. One may well think that the beginning of “encephalitis” was onset of “humoral inflammation” changes, even before cellular infiltration. Generally, encephalitis is detected more sensitively post-mortem or in experimental animals than in clinical patients. But interestingly, there may be unexpected exceptions: Swelling, a classical sign of inflammation, seems hardly detected under the microscope, or was rarely studied specifically. But clinical approach can be sensitive with sophisticated methods: PANDAS apparently represents a (mild) encephalitis underlying long-known tic/obsessive compulsive disorders (OCD) in children [204]. PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) was first described by Swedo et al. as a new disease entity in a subgroup of children who are hypothesized to develop obsessive-compulsive disorder (OCD) and/or tic disorders, having symptom exacerbations following infection with group A beta-hemolytic streptococci. The autoimmune reaction should involve especially the basal ganglia being enlarged during acute disease phases [57]. Mild brain swelling was detected when brain volumes of groups of acutely diseased patients were compared to normal controls, slightly thickened basal ganglia correlating with outbreak of psychopathological syndrome. Preliminary findings in adults suggest similar relationship between streptococcal related mild encephalitis underlying OCD [164]. Of major interest (as from other evidences) for ME hypothesis is, that autoimmune and antistreptococcal antibodies were detectable in part of PANDAS cases but never were sufficient to diagnose encephalitis [204].

Another important point for the clinical situation and ME hypothesis is, that relationship between brain lesions and psychiatric symptoms is weak generally [178, 209], sensitivity and validity of methods therefore being crucial for diagnosis. Reconsidering encephalitis and hypothesizing ME possibly underlying psychiatric disorders of unknown etiopathogenesis therefore needs to take into account all these aspects. Trying to bridge gaps, limitations and inconsistencies of definitions, methods and approaches, a definition of ME (see table 1) can be preliminary only in this situation, a more exact definition expected with increasing knowledge.

ME and psychiatric disorders

Encephalitis is usually differentiated according to specific causes. Nevertheless, in many, especially viral, infections immune mechanisms are important, or can dominate, or determine onset or severity of disease, eg. in BD [25]. Generally, viruses show an affinity to the central nervous system and often latently infect the CNS, presumably because of CNSs low cell turnover and mitigated defense mechanisms [103]. Therefore, viruses and accompanying or viral-induced immune pathology seem of major interest when discussing ME hypothesis, and viral ME may now serves as a model.

Viral ME

Viruses may be implicated in the pathogenesis of psychiatric disorders by various pathways [163, 224]. Latent infections are as frequent as of 80% in old ages in humans [215], though usually nonpathogenic. But latent viral infections in animals may disturb CNS function causing behavioral syndromes even without apparent inflammation [157]. In classical inflammatory viral CNS infections upregulated chemokines and other evolving soluble factors are detected distributed over the brain disturbing brain function when cell infiltrates may be small and localized. However, it is now open when such humoral phenomena are to be termed “inflammatory” [87, 222]. Soluble, disturbing and/or toxic factors may for example explain the observed dissociation between degeneration, inflammation and symptom severity in HIV brain infection [134, 137, 223], which is now increasingly understood as HIV encephalitis (HIVE) not HIV encephalopathy as was previously. However, when defined according to neuropathological consensus criteria (cell infiltrates plus markers) HIVE was detected post-mortem in only 30% of symptomatic AIDS patients, and no HIVE in asymptomatic patients though in 30% within choroid plexus and in 15% within brain HI virus found [165]. Yet, in about 70% of AIDS patients in-vivo CSF findings indicated HIVE according to clinical criteria established in other types of encephalitis [130, 177]. We found similar CSF pathology

Table 1. Preliminary definition of mild encephalitis (ME).
Heterogeneity and non-specificity

Etiology of most psychiatric disorders is not known. Known etiologies are causing variable psychiatric symptoms/syndromes, referred to as non-specificity [27, 98, 32]. Failure of modern diagnostic classifications to improve knowledge about etiologies from a symptom-oriented approach [60, 143, 172], may therefore not be surprising. Non-specificity seems reflected also in continuum or unitary hypotheses of major psychoses [188, 95, 96, 153, 202]. A certain continuum between schizophrenic and affective psychoses and personality disorders apparently exists and fits in with overlap of symptom spectra between disorders [153, 68, 227], with intradiagnostic symptom-syndrome changes during courses [68], and with high risk group findings, eg. schizophrenia families showing increased prevalence of various psychiatric disorders [105], and overlap was recently specified from genetic findings [22].

Known encephalitis

Post mortem studies in cases having died during acute catatonic schizophrenia showed, after careful microscopic examination, mild encephalitis in about 50% of cases [93]. Sporadic encephalitis then was recognized to be easily overlooked respectively difficult to diagnose even in clinical settings [94]. These studies seem especially important and unique, also because as at that time patients relatively often died during severe acute schizophrenic psychoses or so-called pernicious catatonia, a syndrome which has disappeared with the availability of modern neuroleptic treatment and intense care medicine. [Although the reasons for, happy to say, disappearance of pernicious catatonia remain unclear, in retrospect one may suggest that such patients may have died not from encephalitis but from general medical factors not well treatable at that time, such as muscle rigidity and overexcitation, subsequent myolysis and renal failure, hyperpyrexia.]

Beyond any doubt, known encephalitis can cause a spectrum of psychiatric symptoms/syndromes with or without neurological symptoms. In single cases initial personality disorder progressed within days or weeks to affective and later schizophrenic psychosis, eventually organic syndrome. However, diagnosis in such cases was often difficult, convincing CSF or brain imaging findings being present in certain, usually progressed, or initial, stages only [reviews in 13, 70, 94, 128, 207]. How psychiatric symptoms developed from underlying encephalitis remained undefined in any of such cases. Especially initial or intermediate stages of such known rather mild encephalitis fitted in with ME as tried to define her but may demonstrate the top of an iceberg underlying a subgroup of various psychiatric symptoms/syndromes of unknown etiology. However, variable symptoms/syndromes make diagnostic or scientific approach difficult. Independent preexisting liability factors may set another burden for differentiation. But schizophrenia is well investigated and plausibly represents a core syndrome of psychiatric disorder from underlying though mild brain pathology [compare 60]. Therefore ME hypothesis could be repeated in schizophrenia.

Schizophrenia and ME

Etiopathogenesis of schizophrenia is discussed as neurodevelopmental [3] or heterogeneous [69, 28] or both according to the two-hit hypothesis [10]. Neuroleptic treatment improved schizophrenic symptoms but didn’t change overall course considerably [155, 74, 159], suggesting an ongoing underlying disease process. Such could be genetically determined: For example, varying metabolic disturbances accompany progressive brain atrophy in Chorea Huntington [41, 65]. And deteriorating brain function and structure in schizophrenia could fit in with neurodevelopmental hypothesis, but evidence was not conclusive [28, 69, 220] and when brain change occurs remained open [80, 88, 174].

Genetic factors are established important etiologic factors in schizophrenia, but search for single loci was unsuccessful, the overall findings best compatible with complex genetic trait, causing involving important environmental factors [100]. Gene-environmental interaction is known in many infections, especially viral infections. Pre- or perinatal viral infections disturbing neurodevelopment were repeatedly suggested [reviews in 224, 225]. But no major environmental effect has yet been defined, pre- or perinatal environmental insults to the brain can at best explain a small subgroup of schizophrenia, and are not specific [100, 106, 145]. Furthermore, liability precursors do not exclude specific underlying causes [106]. ME from reactivated and/or newly acquired infections could demonstrate such specific underlying “cause”, respectively pathology.

But could ME explain the findings in schizophrenia? Well established are distributed brain atrophy respectively brain volume reduction (deteragative or neurodevelopmental?) and distributed brain functional disturbances [4, 23, 34, 39, 46, 61, 119, 121, 127, 150, 211, 218, 221]. Surely, ME could explain both, brain atrophy and functional disturbance. And even paradoxical findings within studies, apparently not related to methodological differences between studies, would elegantly fit in with ME hypothesis:

1. Slight brain atrophy can apparently progress or accelerate after disease onset [39, 40, 125, 150, 174, 175]. However, involved brain structures were changing over time into two directions: volumes decreased over the long-term in most cases, decrease associated with overall clinical deterioration and in line with this, cases with less overall atrophy did clinically better; but some cases showed larger brain volumes temporarily and in parallel more severe symptoms [40, 55].
2. Although high risk persons showed similar but less reduced volumes of amygdala-hippocampi and thalamus as patients along a gradient from controls to relatives to schizophrenic patients, first episode schizophrenic patients showed thalamic volumes identical to normal controls [119].

3. Cortical, especially orbito-frontal, volume was reduced in schizophrenia, but many first episode patients showed increased orbito-frontal volumes [205].

4. Subcortical volumes of neuroleptic-naïve patients did not differ from healthy subjects except lower thalamic volume; but large thalami and putamina were associated with more positive symptoms [72].

ME could explain such paradoxes: Chronic encephalitis or postencephalitic state could explain overall atrophy from degeneration correlating with severe chronic symptoms; (sub-) acute or reactivated ME could explain large brain volumes by mild brain swelling in recent-onset cases or during relapse phases in disease course associated with acute symptoms or clinical deterioration. Disturbed function and metabolism during ME would just demonstrate another side of mild inflammation, and was demonstrated in various types of encephalitis in animals.

Would age of onset of schizophrenia be compatible with ME? Indeed:

1. Pathogenicity of various viral infections is peaking during adolescence and young adulthood [2; figure], schizophrenia onset is peaking in similar ages [73].

2. Antibody seroprevalences within population indicate (partially) cumulative risk of infections, when over years detectable after acute infections: seroprevalences increase with age when life long risk of respective infection exists [2]. Such seroprevalence curves resemble cumulative schizophrenia incidence (compare figure 73) Similarity and cooccurrence of curves in both entities could suggest a causal relationship: unknown multiple viral infections might underlie schizophrenia. And this would match with the fact that humans are known to acquire various viruses during lifetime, reflected in increased prevalence with older age within post-mortem brains [compare 215]. Age-related variation of pathogenicity in viral infections is explained by developmental factors of the host (only partially defined in viral infections in animals). And indeed, some developmental factor, sex and estrogens, influence schizophrenia onset [73]. One should note in this context, that age of schizophrenia onset cannot be explained by genetic factors [123].

The epidemiology of schizophrenia is well investigated, multiple causes are considered a most likely explanation of [73, 100]: Rather similar occurrence worldwide, similar age-related variation of disease onset, probably life-long risk, rather stable disease frequency within populations despite lowered reproduction rate. Of special interest seem some unexplained findings [100]:

a) High rates in immigrant groups.

![Fig 1. Age-related variation of pathogenicity (diseased per infected cases) and related dynamics of serum antibody prevalence in population in viral diseases and possible analogy to schizophrenia epidemiology](image)

- **a**: Risk of complications, *a1*, including encephalitis, *a2*, in mumps virus infection [2]. Pathogenicity of BDV for humans is undetermined but assumed increased in young ages because BDV seroprevalence in psychiatric inpatients aged 17-30 years was increased compared to surgical controls (OR=6.8) [see 18]; increased (psychiatric) pathogenicity plausibly would increase risk of psychiatric hospitalization

- **b**: Mumps seroprevalence in population [2] or BDV seroprevalence in surgical controls [18].

**Interpretation:**

**a1**: Curve *a1* resembles age-related variation of schizophrenia onset (compare 73). MEs from various etiologies represented in curves similar *a2* might cumulating shape or contribute to a curve similar *a1*.

**a2**: Curve *b* represents cumulative net effect (+ newly infected cases, - lost serum antibodies) characteristic for viral infections with long life. Similarity to cumulative schizophrenia incidence is striking (compare 73).

**a1+b**: Similar age-relatedness and combined occurrence of respective curves in schizophrenia onset/incidence or viral infections pathogenicity seroprevalence could indicate a common causal background

- **b**: Urban birth or urban residence as risk factors.

- **c**: Season of birth effect. These three factors may suggest viral etiology, possibly pre- or perinatal [145, 146, 208]. But adolescent/adult viral ME would fit in with the three findings: season of birth with increased risk of later reactivated ME after pre- or perinatal infection, urban residence and immigrant status with recently acquired ME or reactivated ME correlating with increased risk to acquire viruses in high population density or when contacting new infectious agents within new population.

**Schizophrenia onset** is often protracted over years, disease courses being acute, subacute, remitting-relapsing or slowly
progressive [67, 73, 99]. Similar onset and disease course patterns are known from immune pathologic disorders [102].

Immune abnormalities and altered inflammatory mediators were found in schizophrenia and affective psychoses [reviews 122, 124, 132, 149, 169, 171], and could link to ME.

Earliest symptoms in schizophrenia are mostly non-specific [74], and in 30% headaches [135], both compatible with ME (compare initial stages of known meningoencephalitis). The basic symptoms concept developed by Gerd Huber specifically addressed those aspects of non-specificity, prodromal symptoms and related transitions into acute disease stages [71, 97], and a recent remarkable catamnetic study over 10 years showed that prodromal basic symptoms fairly predict later schizophrenia [114].

However, a series of recent findings can be considered well compatible with or even supporting ME hypothesis underlying a subgroup of schizophrenic and affective disorders: 1. Post-mortem brain findings in schizophrenia and affective disorders (see table 2). 2. Clinical findings in schizophrenia and affective disorders (see table 3). 3. Findings in BDV seropositive psychiatric patients, especially within the schizophrenic subgroup (see V).

Nevertheless, many of these findings are subject to ambiguous interpretation, for example.

1. Neurontmitter abnormalities and phospholipid metabolism disturbances were interpreted as primary infection abnormalities [92], but could be secondary from ME. Similarly, therapeutic effect from substitution with free fatty acids (FFA) could relate to genetically determined membrane defect and vulnerability improved by forced substitution or to antiinflammatory action of FFA [compare 131]. Similarly, degeneration and regeneration of motor neurons observed in up to 50% of patients with schizophrenic or affective disorders may relate to primary membrane abnormality [50, 51], or be secondary from inflammation or toxic insults [37, 139].

2. Another example is preliminary findings on retroviruses and microglial activation or 'inflammatory' mRNAs (compare table 1 and 2). Retroviruses might be triggers, precipitators or markers of inflammation [compare 21, 129, 162]. Interaction between genetic and immunological factors in CNS disorders is complex [6]. Viral infection can shift to autoimmune CNS disease in experimental animals [158, 182]. Accompanying autoimmune aspects were demonstrated in several human CNS infectious disorders, even bacterial eg. Lyme disease [79, 113]. So, what was first can be difficult to decide in manifested human disorder.

3. Another example is interpretation of CSF findings: CSF flow was reduced in 20% of randomly collected schizophrenic patients [161]. Independently, CSF protein was found slightly increased in 20-40% of patients during acute schizophrenic psychoses, interpreted as blood brain barrier (BBB) disturbances [147]; and in patients with protein increases CD4 cells and adhesion molecules were found more often [148]. Now it was understood in neurological patients that CSF protein increases may not indicate BBB disturbance or blood CSF barrier (BCB) disturbance, but instead result from reduced CSF flow [176, 177], which is known to occur in meningoencephalitis [compare 161]. Findings on CSF cytokine abnormalities or mononuclear macrophages accumulated within CSF

<table>
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<tr>
<th>Finding(s)</th>
<th>Author(s)</th>
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<tr>
<td>Aberrant mRNAs in about 1/3 of cases</td>
<td>Yolken et al 2000 [review, 225]</td>
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<tr>
<td>Aberrant proteins, mainly GFAP isoforms</td>
<td>Johnston-Wilson et al 2000 [104]</td>
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<tr>
<td>Microglial activation in about 40% of cases</td>
<td>Bayer et al 1999 [11]</td>
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<tr>
<td>Neuronal cell membrane abnormalities*</td>
<td>Uranova et al 2000 [210]</td>
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<tr>
<td>Structural abnormalities of subicular dendrites</td>
<td>Rosoklja et al 2000 [181]</td>
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<tr>
<td>Hippocampal synaptic pathology</td>
<td>Eastwood and Harrison 2000 [45]</td>
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<td>Decreased dendritic spine density on prefrontal cortical pyramidal neurons</td>
<td>Glantz and Lewis 2000 [59]</td>
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*) Blood serum fractions of patients elicited similar membrane abnormalities in-vitro, rather suggesting some soluble 'toxic' factor [33]

Table 2. Selected brain post-mortem findings in schizophrenia and affective disorders compatible with ME hypothesis.
during acute psychoses in a subgroup of schizophrenic patients (table 3), add further evidence to interpret these findings as indicative for ME.

4. Decreased dendritic spine density could in part be explained by decreased (mainly thalamic) inputs and plasticity, but overall was suggested that, like many other observation and post-mortem studies (alterations in gene expression and neurotransmitter receptor) may not reflect a fixed lesson in the DLPFC of schizophrenic subjects [59] - "Inflammatory" humoral factors including such as QYNAD (see below) could be related to dynamic cellular pathology. - (Not discussed here are replicated findings of reduced neuronal cell body sizes, which may be independent trait markers from neurodevelopmental origin or could represent a consequence of chronic ME).

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<th>Findings(s)</th>
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<td>Evidence of autoimmunity</td>
<td>Ganguli et al 1987 [review, 54]</td>
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<tr>
<td>Cellular and humoral immune abnormalities</td>
<td>Müller et al 2000 [review, 149]</td>
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<tr>
<td>Slight CSF protein increases (in one study correlated with T cell molecules during acute psychosis), or activated macrophages</td>
<td>Müller et al 1991 [147]</td>
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<td>Kirch et al 1992 [112]</td>
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<td>Pitts et al 1990 [168]</td>
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<td>Schweitzer et al 1999 [190]</td>
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<td></td>
<td>Nikiel et al 1999 [154]</td>
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<tr>
<td>Reduced CSF flow in 20% of randomly collected schizophrenic patients</td>
<td>Oxenstierna et al 1996 [161]</td>
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<tr>
<td>Heat shock proteins (cellular or humoral reactions against)</td>
<td>Leykin et al 1999 [122]</td>
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<td>Kilidireas et al 1992 [111]</td>
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<td></td>
<td>Schwarz et al 1998 and 1999 [189, 190]</td>
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<td>Retroviral sequences in CSFs of about 45% recent onset schizophrenia patients versus 17% of controls</td>
<td>Karlsson et al 2001 [109]</td>
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<td>Anti-retroviral serumantibodies (in about 30%)</td>
<td>Hart et al 1999 [75]</td>
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<td>Lillehoj et al 2000 [126]</td>
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<td>Endocrine and cytokine abnormalities</td>
<td>Katila et al 1999 [110]</td>
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<td>Anisman et al 1999 [5]</td>
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<td>Arolt et al 2000 [7]</td>
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<td></td>
<td>Licinio and Wong 1999 [review, 124]</td>
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<tr>
<td>Virus-like agents isolated from CSFs during acute psychoses</td>
<td>Rott et al 1991 [184]</td>
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<td></td>
<td>Hinze-Selch et al 2000 [89]</td>
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<tr>
<td>Skeletal muscle atrophy in up to 50% of schizophrenic or affective disorder</td>
<td>Meltzer 1973 [139]</td>
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<td>Crayton and Meltzer 1979 [37]</td>
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<td></td>
<td>or Flyckt et al 2000 [51]</td>
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<tr>
<td>Therapeutic effect of fatty acids</td>
<td>Horrobin 1998 [92]</td>
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<td>Maes and Smith 1998 [review, 131]</td>
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<td>Immunological effects of clozapine</td>
<td>Maes et al 1994 [132]</td>
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<td>Jones-Brando et al 1997 [107]</td>
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<tr>
<td>Effects of antipsychotic drugs on cytokine networks</td>
<td>Pollmährer et al 2000 [review, 171]</td>
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Table 3. Clinical findings in schizophrenia and/or affective disorders compatible with ME hypothesis.
In sum, ME from viral or retroviral infection with single or coinfective multiple agents or autoimmune ME induced by viruses and modulated by developmental host factors could well explain a subgroup of cases of schizophrenia (and likely part of affective and spectrum disorders not discussed in detail here) on the levels of symptoms, epidemiology, course, findings on brain volumes, disturbed function and metabolism. ME is understood as the basic pathophysiological process though within a complex immune-genetic multifactorial framework. Type and severity of clinical symptoms in individual cases might over this be influenced by independent preexisting factors.

Diagnosing encephalitis

Characteristic clinical symptoms (fever, meningism, focal neurology, disturbed consciousness, seizures) suggest (meningo-) encephalitis, diagnosis established by CSF investigation, supported by imaging or EEG. MRI is sensitive in some types, eg, herpes simplex virus encephalitis (HSV), SSPE or multiple sclerosis, however in lymphocytic meningitis usually normal [160]. In Creutzfeldt-Jacob disease or Japanese encephalitis non-specific MRI lesions are frequent, representing small liquid filled vacuoles [48, 142]. In HIV infection often only brain atrophy is visualized [160], although mild inflammation is common histologically [reviews in 173]. TSE and F-FLAIR MRI detect more lesions below 5 mm diameter than conventional MRI [185]. But considering that inflammatory brain lesions for example in BD (rats, primates or horses) are macroscopically invisible and prefer gray matter [152, 198], present MRI methods appear insensitive in hypotonic human BDV ME. In fact, gray matter inflammatory lesions are nearly never detected by MRI [160].

Estimating sensitivity of modern CSF diagnostics in ME

Seroconversion or increasing serum antibodies paralleled by increased cell number and/or protein contents in CSF indicate (meningo-) encephalitis. New methods improved sensitivity and specificity, especially PCR [215] and simultaneous analyses of proteins in blood and CSF, controlling for blood-brain barrier (BBB), respectively blood-CSF barrier (BCB) function [reviews in 47], respectively reduced CSF flow [176]. Brain specific ‘inflammatory’ molecules can help diagnosis.

Bacterial (meningo-) encephalitis is sensitively diagnosed, normal CSF usually considered excluding. However, a recent rare study, unique with modern methods, challenged even this assumption [56]: ventricular and lumbar CSF's simultaneously investigated showed high variation, lumbar CSF showing less or much less pathology; eg, no cells despite pus on hemispheres. [Vice versa, in Guillain-Barré syndrome proteins are increased in lumbar but normal in ventricular CSF [47, 176].

In viral CNS infections PCR is considered sensitive. For example, positive predictive value in HSVE was calculated 95-100%, negative 98% [review in 215]. However, HSV DNA detection in CSF correlated poorly with clinical symptoms as with MRI findings as with outcome [217] and differed in different stages [9, 144, 170, 193], studies often suffering from ascertainment bias of mild cases [9]. Further details suggest caution:

1. PCR in definite HSVE was discrepant from 2 laboratories in 18% of cases [90].
2. Although HSV DNA was detected in both, severe HSVE or no HSVE according to MRI, PCR was negative or CSF proteins normal in 20% severe HSVE [52].
3. Multiplex PCR detected causal viruses in aseptic (likely viral) meningoencephalitis only in 35% [35].

So, does negative PCR with ‘moderate confidence’ [101] exclude viral CNS infection? In 80% of definite meningoencephalitis causal virus was detected by CSF PCR, but only in 20% of ‘probable’ cases showing meningism, fever, headache and/or CSF cell count increases (according to this definition) and representing most cases [compare 101].

In another rare study the question of sensitivity of CSF diagnostics in viral encephalitis was specifically addressed: Within CSF, JEV DNA concentration was much less than within brain in a range of about four orders of magnitude, and virus load in CSF variable during comparable disease states [44]. In slow virus infections lumbar CSF is often normal [215], though brain histopathologic changes severe.

In viral CNS infections in animals, inflammatory processes often exceed distribution of viral antigen [58, 66, 156], or viral burden can decline over time when inflammatory phenomena and chemokine upregulation persist causing chronic disease or even progressive neuropathologic abnormalities [81, 140, 141]. In astrocytes cell cultures sustained expression of Tax-1 was found associated with secretion of inflammatory mediators when virus replication was only short-lived, presumably explaining the difficulty to detect viral product in post-mortem specimens from human HAM/TSP patients [206].

Summing up: Sensitivity of available diagnostic methods appears rather low or insensitive to detect ME as described here. Sensitivity of CSF diagnostic methods depends from localization, accompanying meningitis or radiculitis, overall severity of disease, specific agent, time point of investigation relative to symptom onset, and immunological factors of the host. Normal findings in lumbar CSF do not exclude ME. Viral infection could elicit ME: initial short-lived (mild) cellular inflammation might be followed by sustained humoral ‘inflammatory’ upregulation, or autoimmune shift (see below).

Borna Disease (BD)

BD is a (meningo-) encephalitis caused by a neurotropic negative-stranded RNA virus [38], earlier described in Middle Europe in horses and sheep, but may be wider distributed, possibly worldwide; many species can experimentally be infected [183, 203]. After BDV infection immunocompetent
animals develop an encephalitis mediated by CD4+ and CD8+ cells [25]. Symptoms and course are variable, dependent on genetic factors, immune status, and age of the host, species, virus strain, route of infection, dose of infectious virus [86]. Cellular inflammation is accompanied by distributed neurotransmitter alterations, chemokine upregulations and even toxic factors during evolved 'inflammation' contributing to variable symptomatology [42, 58, 180, 194, 195, 196, 197]. Perinatal BD shares phenomena of BD in immunocompetent animals depending from time point of infection after birth [83, 91, 152]. Perinatal BD induces brain developmental abnormalities [43, 91, 186]. Accordingly. two basically different models of human BD are discussed [13, 29]. Briese et al preferred perinatal BD, arguing that it was difficult to establish direct parallel between adult BD models in animals and a single human CNS disorder. But this appears at least similarly difficult for perinatal BD. And when 'marked CNS inflammation in adult-infected rats makes it difficult to determine whether monoamine, cholinergic, and opioidergic function in BD results from direct effects of the virus, virus effects on resident cells of the CNS, or a cellular immune response to viral gene products' [29], another point is highlighted: research on BD preferred animal models with marked inflammation from obvious reasons. But these models nor may allow refined differentiation of neurotransmitter alterations nor may provide best models for human psychiatric disorder. However, one study on BD in low primates was very interesting: mild, macroscopically invisible cellular inflammation preferably of the limbic system correlated in 20% of infected animals with overt disease including neurological symptoms (paresis), but in 80% with exclusive abnormalities of complex behaviors; furthermore, some animals showed a type of behavioral 'defect' after and/or relapsed years after [188]. Such model shows considerable analogy to human psychoses, be it affective or schizophrenic, and could fit in with our findings of a possible ethiopathogenic role of BDV in psychiatric and some neurological disorders [13, 14]. Similarly interesting was a BD obesity rat model: cellular inflammation and virus replication were short-lived after infection but humoral 'inflammatory' upregulation sustained [81]. But even BD rat models with 'marked' inflammation show interesting analogies to psychiatric disorders when just assuming inflammation to be mild; prefrontal cortex dysfunction, phasic hyperactivity, psychomotor slowing, defect, dyskinesia, dystonia, behavioral and biochemical hypersensitivity, neurotransmitter alterations, genetic contribution [42, 58, 84, 86, 152, 194, 195, 196, 197, 198]. Some other findings appear interesting regarding BDV ME hypothesis: T cell ignorance during persistent Borna virus infection of the brain can be overcome (and encephalitis induced) from antigenic stimulation at peripheral site [77]. Nonlytic chronic BDV infection reduced ability of glutamate uptake (and to prevent neuronal excitotoxicity) of astrocytes in vitro [24].

Overall, there is no proof of human BD yet and it remains debated what, if any, human disorders may result from BDV infections [17, 18, 26, 62, 76, 86, 179]. Apparently a considerable part of the discussion can be related to low replicability of some methods, especially nested RT-PCR or RT-PCR at least in available studies [191, 192, 199]. Replicability in serological studies was better [199], rather supporting so far our earlier view [86, 179]. A recent paper may help solving part of the discussions: 30-50 days after intracerebral infection of rats BDV nucleic acid was detected in blood, neutralizing antibodies developed between 60 and 100 days after infection, appearance of antibodies indicating chronic infection according to the authors [33].

Facing these open questions it seems appropriate to restrict discussion here on findings based on serological studies in humans. Serological tests used in our human studies were in parallel used in animals over many years: comparing serological findings in sera and CSFs with post-mortem findings from brains of horses naturally diseased (n=170), high sensitivity and specificity of methods in the horse system was demonstrated [85 and unpublished]. Sera of over 15,000 humans were investigated, individual patients replicably identified seropositive over many years [13]. Nevertheless, whether BDV or a related agent or another immune cell might have induced human BDV reactive antibodies remains yet open [1].

Our interpretation of a possible human BD was: BDV seroprevalence was found increasing with age in surgical controls and in neurological patients interpreted as indicating a life long risk to become infected by BDV [18]. In psychiatric patients BDV seroprevalence was significantly increased, yet in young patients [18]. Diagnosis patterns in BDV seropositive psychiatric patients were similar to seronegative psychiatric controls, but psychiatric comorbidity and drug addicts more frequent in psychiatric seropositives. Drug addicts acquire various viruses preferentially. Disregarding drug addicts, BDV seroprevalence remained significantly increased in psychiatric patients (OR=6.8 in ages 17-30 years, OR=1.7 in ages 31-50 years), and comorbidity increased in seropositives. Further characteristics in BDV seropositives were: more schizophrenia deficit syndromes respectively worse courses [18, 212], more frequently sight brain atrophy [15, 212], more frequently coexistencies and shift to psychosis [13]. CSF investigations showed direct evidence of BDV ME in some patients: From CSF of one BDV seropositive schizophrenic patient a BDV-like viral agent was isolated [184] and BDV specific immunoglobulin G found intracereally produced during acute psychosis, but not 5 years later [17]. In 12-25% of (n=38) BDV seropositive cases BDV specific immunoglobulin G was found intracereally produced during acute schizophrenic or affective psychoses; this suggested underlying BDV ME [16]. Similar minor CSF pathology (= increase of agent-specific IgG within CSF) was described in encephalitis with neurological symptoms [130, 144, 170, 177]. In single BDV seropositive cases CSF proteins were considerably increased in short time frames during acute psychosis [compare 19]. Our hypothesis of BDV ME was recently corroborated, when detecting QYNAID increased within CSFs of BDV seropositive patients with schizophrenia or affective psychoses [19, 20]. QYNAID, an antinociceptive endogenous peptide, was earlier found increased in various neurological inflammatory CNS disorders including Guillain-Barré syndrome (GBS) [8, 30, 115, 216], and in preliminary studies, when patients with therapy resistant presumably
BDV ME-related schizophrenic or affective psychoses improved impressively after cerebrospinal fluid filtration (CSFF) [19, 20]. CSFF therapy is performed in various infectious or autoimmune CNS inflammatory neurological disorders [31, 49, 108, 166, 167, 200, 219].

**Summing up:** BDV or a related agent presumably can infect humans, but seroepidemiological and clinical studies need replication and confirmation, and interpretation remains controversial. In this authors view BDV ME (defined accordingly to table 1) seems a plausible explanation of at least own findings. BDV ME may be reactivated or newly acquired. Because BDV seroprevalence was increasing with age in surgical and neurological controls, new infection within human population from infancy into adulthood and into old ages seems prevalent. Various psychiatric syndromes could be explained by BDV ME, preferably schizophrenic and affective disorders, type of syndrome influenced by independent liability factors. Spectrum personality disorders and rarely BDV meningencephalitis with neurological symptoms may occur. Extrapolating from own findings, 3-10% of psychiatric disorders in our clinic could be related to BDV infection. Overall pathogenicity of BDV for humans seems low, less than 10% of infected people developing symptoms [18].

**Discussion**

Considerable similarities exist between slow encephalitis and encephalopathy, but there is an important difference for therapy and prevention, as demonstrated in HIV brain infection in [173] or prion diseases [78]. Differentiation between inflammation and degeneration, or between genetic and infectious causes were old problems in neuropsychiatric research, eg. in general paresis [12]. Progress to understand slow infections underlying neuropsychiatric disorders was accomplished only by new basic research overcoming false old dogmas. Such may evolve: virus-induced autoimmune diseases have been recognized recently but complicated interaction is just begun to be understood [82, 116, 117]. An interplay of similar factors appears in infectious diseases, in inflammation itself, in neurodevelopment, and in specific pathways within the nervous system [138, 226]. Immune activation and molecular mimicry import an important role for inflammation/degeneration but also for persistence of agents within CNS [79, 158]. A wealth of non-specific 'inflammatory' molecules was recently identified during viral CNS infections [87, 222], but their meaning and applicability in human diagnostic approaches is widely open [118, 120]. Disturbing and even neurotoxic factors can evolve during viral infections in humans, eg. HIV infection [137, 223], explaining part of clinical symptoms in inflammatory or neurodegenerative neurological diseases [30, 214]. But psychiatric disorders are just begun to investigate.

Mild microglial activation may represent a chronic inflammatory reaction of the CNS [11, 36]. Aberrant repair mechanisms may play a pathogenic role [201]. Synaptic pathology found in schizophrenic brains [45], may resemble synaptic pathology in viral infections [63]. Physiological cell generation and migration within adult primate brains [64], or in-situ neurogenesis after damage [133], both could be disturbed from ME, and such might explain post-mortem brain findings in schizophrenia and affective disorders earlier understood exclusively within a neurodevelopmental framework.

Influence of environmental factors has been clearly documented in schizophrenia (and less important in affective disorders) [224], attributable risk in schizophrenia was calculated 35% [146]. A role for infectious agents, especially viruses seemed plausible [145], but adolescent-adult viral infection is not seriously discussed. But, ME from adolescent-adult new infection or reactivation after earlier infections fits in with many clinical and epidemiological aspects of schizophrenia. Especially the unexplained age-related variation of disease onset in schizophrenia (and rather similar in affective disorders), could be explained by viral infections showing age-related variation of pathogenicity.

Varying weights of interacting hereditary and environmental factors could explain individual variation: such have been disentangled recently in long known disorders: 1. A 1st human autoinflammatory disorder was described: genetic factors determine disease but cyclic inflammation is triggered from unspcific infections or factors [136]. 2. Whether monocytic twins were concordant or discordant for HAM/TSP depended from both, pathogenicity of HTLV I virus strain and HLA alleles, explaining similarly disease patterns within families [151].

Complex interactions between virus, viral factors, virus-induced autoimmunity, genetic and other preexisting factors are assumed in ME hypothesis of psychiatric disorders. Present neuropathological definition of encephalitis with detectable cellular inflammation in the brain is challenged, especially from a clinicians point of view. ME as preliminarly defined here could underlie psychiatric disorders of yet unknown etiology, especially a subgroup (large or small in size?) of schizophrenic and affective disorders, though remaining undiagnosed by available diagnostic methods.

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**Correspondence address:**
PD Dr. Karl Bechter
University of Ulm
Department Psychiatry II
Ludwig-Heilmeyer-Str. 2
89312 G"unzburg/Germany
Tel.: +49-8221.962560
Fax: +49-8221.962400
E-mail: dr.bechter@bih-guenzburg.de
K. Becker: Mild Encephalitis Underlying Psychiatric Disorder - A Reconsideration and Hypothesis exemplified on Borna Disease


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K. Bechter

Dept. Psychotherapeutic Medicine and Psychosomatics (head PD Dr. K. Bechter) of Dept. Psychiatry II, University of Ulm (head Prof. Dr. R. Schlüttler), Bezirkskrankenhaus Günzburg (Germany)