



Mild encephalitis

Theory becomes reality in the emerging field of immuno-psychiatry

- For three decades, Professor Dr Karl Bechter, head of the psychoimmunology working group at Ulm University, Germany has been at the forefront of neuropsychiatry and the emerging discipline of immuno-psychiatry.
- Through clinical experience and research, he proposed the mild-encephalitis hypothesis for a spectrum of severe mental disorders (SMDs).
- This paradigm acknowledges the co-existence of neuroinflammation and immune irregularities in a subgroup of patients with SMDs.
- Such novel thinking and Bechter's contribution to the field catalysed development of diagnostics and therapy options for these conditions.

Psychiatric disorders are classified as either primary or secondary diseases. The causes of primary disorders are unknown whereas secondary diseases have clear causes such as trauma, hypoxia (insufficient oxygen supply to the brain) or infection, to name a few. Infection-related causes of severe mental disorders (SMDs) have become increasingly recognised, as has a link with inflammation and immune abnormalities. Professor Dr Karl Bechter of Ulm University, Germany has recently published an article in the *Journal of Affective Disorders Reports* that brings together 30 years of neuropsychiatry data to review the development of this field and the status quo.

An emerging and fascinating branch of neuropsychiatry is immuno-psychiatry (IP). As implied in the name, IP is where the immune system and central nervous system (CNS) influence each other. This could include immune dysfunction that causes psychiatric disorders or immune disorders presenting in psychiatric patients. With increased recognition of the role of immune system dysfunction in psychiatric disorders, a major shift in psychiatry is the development of immune-based therapies to treat these disorders. Examples include the use of anti-inflammatory drugs in schizophrenia, severe depression, and bipolar disorder.

Mild encephalitis at the heart of it all

Recent work has identified that neuroinflammation plays a key role in a range of severe mental disorders (SMDs). Linked to this is what is known as the mild-encephalitis (ME) hypothesis. Originally proposed by Bechter in 2001 and updated 12 years later, it suggests SMDs including mood disorders and schizophrenia are caused at least in part (subgroup) by mild neuroinflammation triggered by infections or autoimmune processes, trauma, and other factors. This theory

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is gaining popularity with supporting evidence including increased immune cells and inflammatory markers in the postmortem brains of sufferers. In fact, Bechter suggests that up to 40% of schizophrenia cases might be linked to ME.

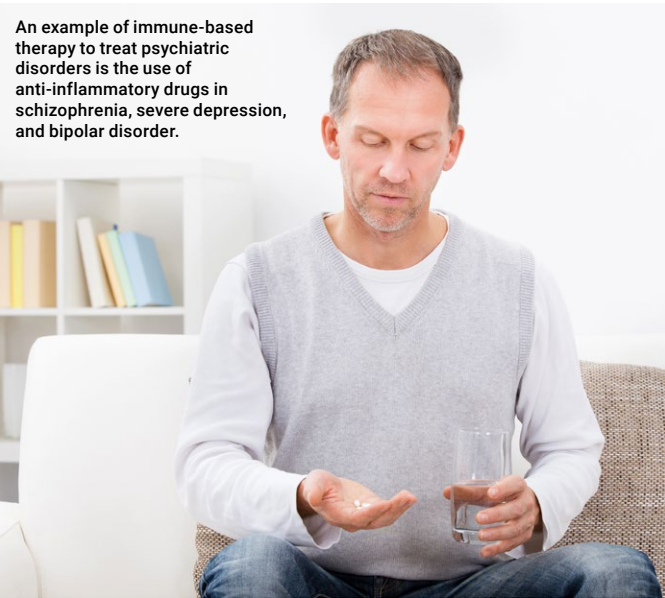
More recently, the spotlight has turned to autoimmune encephalitis (AE). Simply put, AE is when the body mistakenly attacks its own CNS cells, thinking they are a foreign invader. The cause can be cancer, or is often unknown, but could be related to initial infection insults. Presentation can be very similar to other psychiatric disorders, such as schizophrenia or even dementia. Clinicians may turn to analysing cerebrospinal fluid (CSF) to help differentiate AE from other disorders because this subgroup often benefits from drugs that modify the immune system (immune modulatory treatments).

Another condition under study in IP is autoimmune psychosis (AP). Experts agree that an overlap can exist between AP and AE, although many believe AP is a separate disease. Central to their diagnosis is the detection of autoantibodies (antibodies produced by the body against its own proteins) in CSF. These autoantibodies cause neuron dysfunction and patients present with psychosis (psychological state where patients lose sight of reality, become delusional, and may hallucinate) and cognitive impairment, ie, typical symptoms of AE presenting with various, and often, severe neurological symptoms.

Recent international consensus on the topic provides much-needed guidance for diagnosis, detailing therapeutic options and highlighting the urgent need for further studies and clinical trials to improve diagnostics and test new drugs, respectively. Immuno-psychiatry also encompasses autoimmune depression and autoimmune obsessive-compulsive disorder (OCD), with existing evidence for some cases of OCD being of autoimmune origin or triggered by infections.

Diagnostic tools: The value of CSF

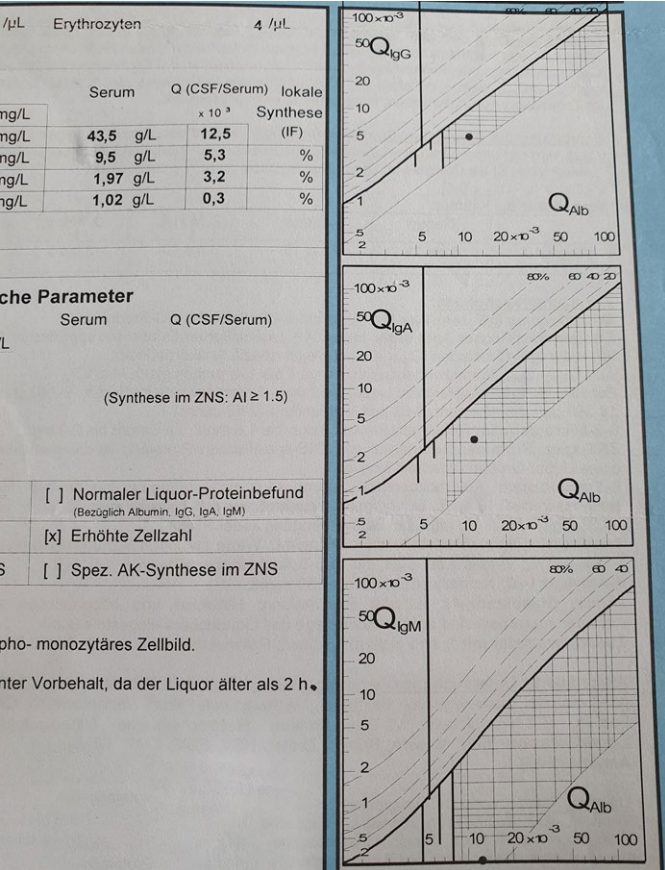
Cerebrospinal fluid (CSF) present in the tissues surrounding the brain and spine offers mechanical protection for these vital organs. Extracted from the lower spine during a lumbar puncture, this clear fluid consists of water, proteins, glucose, ions, and neurotransmitters (which aid communication between the CNS and other bodily



systems). CSF also serves to maintain homeostasis, supplies vital nutrients to the CNS, and clears waste. A newer insight was that the CSF spaces act as a ‘gating area’ in CNS immunity.

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Example of an abnormal CSF result in SMD patient with slightly increased cell number and increased immunoglobulins G and A, analysed by Reibergrams, indicating mild encephalitis. For more general information on CSF analysis, see doi.org/10.1007/978-3-662-68136-7.

the 1990s. CSF diagnostics are more advanced in some areas, such as dementia, than other SMDs. Large studies have provided insight into how CSF proteins in SMDs differ, but what these abnormalities mean and how they translate clinically are unclear and require further research. In as many as 40% (or more depending on the methods used) of SMD cases, in particular schizophrenia and mood disorders, minor CSF abnormalities have been documented. Such findings highlight that CSF contains information that could be valuable in psychiatric disorders.

An area where the sensitivity and relevance of CSF diagnostics in SMDs is apparent is in AE with prominent psychiatric symptoms, specifically AP: one study showed if CSF analysis had not been performed, 14% of cases would have been mistaken for schizophrenia and not classified as AE/AP. More concerning is that these patients would have missed an opportunity for immune-based therapy which has proven to be successful in many patients.

CSF registry: The way forward?

A study by other researchers published this year examined CSF in over 500 SMD patients (broadly repeating results of Bechter, et al, 2010) advocating its utility in newly diagnosing conditions like multiple sclerosis (MS) and encephalitis including autoimmune encephalitis. The authors called for CSF to be considered in any patients unresponsive to treatment and presenting in a nontypical way. They have started a CSF registry to determine what abnormal CSF values in psychiatric disorders are so this diagnostic tool can be refined.



The field of CSF diagnostics has gained real traction over the past few decades, with Bechter being a driving force in this area since the 1990s.

With about twenty autoantibodies discovered so far relating to psychiatric disorders and the advent of CSF registries, research in this area is rapidly developing, but challenges remain. CSF diagnostics are not commonplace worldwide and many countries still consider it unethical. With a recommendation by a leading psychiatric association for CSF diagnostics in schizophrenia and its utility in early MS detection, Bechter argues the importance of CSF diagnostics can no longer be disputed. However, more research is needed into its use in differentiating secondary mental disorders.

As evidence builds, Bechter is optimistic for the future of neuropsychiatry with IP at the helm of SMD research. His extensive publications have led to new insights in IP at key points throughout its journey. But still so much remains to be learnt about the causes of SMDs, despite mounting evidence that mild neuroinflammation and immune activity play at least some part in their pathology for a subgroup of patients. As our understanding of these causes improves, Bechter hopes that advances in immuno-psychiatry will unveil new therapies for the benefit of psychiatric patients worldwide.

Personal response

Can you tell us about any things that have surprised you during your lifelong career in neuropsychiatry and immune psychiatry?

As a young researcher collaborating with established virologists, we had seemingly spectacular findings with high-impact publications about possible viral causes of SMDs and experienced a hype of research on the theme worldwide. But similarly, we saw a rapid decline of interest when the understanding of detailed pathogenesis was not simple and causality conclusions were difficult, requiring a deeper understanding of the whole complexity. The same experience parallels in the clinical field – the interest was high only for simple solutions but not for the obvious, considerable, and therefore, difficult to study variance of symptoms related to some difficult-to-diagnose and newly defined CNS pathology. Neuroinflammation as an entity is widely unknown/unrecognised by psychiatrists. A difficulty was (and still partly is) the funding for such a research focus over the years.

With more to be learnt about CSF abnormalities, their diagnostic potential, and clinical relevance in SMDs, what do you think is key to moving the field forward?

My advantage was that pioneering CSF researchers in neurology, Professor Hansotto Reiber and his pupils Professors Hayrettin Tumani and Markus Otto, agreed to cooperate to develop psychiatric CSF analysis further. A close interaction with CSF researchers in neurology is continuously required as the advantage in neurology is the comparably clear symptom patterns and insight from a broad experience with, and knowledge about CSF diagnostics. To take up this knowledge, improve, and refine it further appears pivotal to me:

the pathological processes in SMDs with mild neuroinflammation are apparently less severe when compared to classical (not mild) neuroinflammatory diseases with neurological symptoms. Therefore, SMDs require more refined methods for diagnosis, built on the extended knowledge from neurology.

What advice would you give a young researcher who is interested in getting started in your field?

Please differentiate between neuroinflammation versus peripheral inflammation, which can occur together, but is not necessarily the rule – at least not as often. Complex clinical approaches plus research are generally required, such as the differential diagnostic approaches published recently (Endres, et al, 2020), because of the heterogeneity of (partial) causes and emerging and evolving details in pathology (over time).

For future CSF diagnostics: the basis is the advanced methods of analysis and interpretation of CSF findings, a complicated field because of the influences of CSF flow onto the single CSF values. This requires a broad learned approach for refined understanding and interpretation (Wildemann, et al, (2010) Laboratory Diagnosis in Neurology). Even many international publications on CSF findings from neurology use rather simple methods, analysis, and interpretation. This may not be that surprising as the field is rather new. The first official CSF Society was founded in Germany (DGLN) in 1991, and the International Society for CSF analysis and Clinical Neurochemistry was founded even more recently, in 2015.

Details



e: karl.bechter@bkh-guenzburg.de
t: +49-15779325496
w: www.uniklinik-ulm.de/psychiatrie2

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Bio

Professor Dr Karl Bechter obtained his license and doctorate in medicine from Ulm University in 1977. He has served as clinical research assistant in neurology and then as clinical research assistant in the Department Psychiatry and Psychotherapy II, Bezirkskrankenhaus Günzburg, University of Ulm. He has been approved specialist in neurology and psychiatry, and specialist in psychotherapeutic medicine. Bechter has served as professor of psychiatry and head of department of psychotherapeutic medicine and psychosomatics in the Department Psychiatry and Psychotherapy II at Ulm University. Now retired (2015), Bechter continues his research.

Further reading

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