S-66-04

Clinical and psychosocial factors predicting response to prophylactic lithium

W. Greil, N. Kleindienst. *Ludwig-Maximilians-Universität, München, Germany*

Objective: Recent randomized clinical trials have shown that lithium continues to be an excellent treatment option in the prevention of manic-depressive episodes. Given the burden and risks related to a long-term treatment with lithium and given the increasing number of alternative mood-stabilizing treatments it would, however, be highly desirable to individually predict response to prophylactic lithium.

Methods: A systematic review was carried out in order to integrate the available evidence on response prediction to prophylactic lithium based on clinical and psychosocial factors. On the basis of the variables identified as potential predictors in this systematic review, an easily applicable prognostic instrument was developed. Finally, validity of this "Lithium Response Scale" (LRS) was evaluated in an independent sample of n=86 bipolar patients prospectively followed up for 2.5 years.

Results: The systematic review identified 21 variables as potentially predictive for response to prophylactic lithium. Based on these potential predictors hospitalization under lithium was correctly predicted in 75% of the patients (AUC=0.72, $p<0.001$; $f=0.35$, $p=0.008$).

Conclusion: These findings suggest that it is possible to predict effectiveness of prophylactic lithium to a clinically significant extent. The instrument used for prediction - the LRS - is open for further improvement - e.g., by integrating biologic and genetic variables in order to enhance its predictive power.

S-66-05

Treatments for different presentations of bipolar disorder

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Objective: Treatments for Different Presentations of Bipolar Disorder The manic presentation responds to antipsychotics, lithium, valproate or carbamazepine; bipolar depression responds to old and newer antidepressants, and to treatments including lithium, lamotrigine and the atypical antipsychotics quetiapine and olanzapine. Special treatment is needed for mixed states, psychotic mania or depression, rapid-cycling, co-morbidity with substance misuse and co-morbidity with other diagnoses such as anxiety states. Even large clinical trials are often insufficiently "powered" to demonstrate efficacy in sub-groups of manic or depressed patients. However efficacy has been demonstrated for mixed manic states with certain atypical antipsychotics. Some evidence suggests differential efficacy of valproate over lithium in mixed mania. Classical antipsychotics are more effective in reducing psychotic mania than quetiapine or olanzapine. Psychotic mania is equally responsive to valproate and to antipsychotics. Non-psychotic mania responds better to an atypical antipsychotic than to a classical antipsychotic or to valproate. Studies of prophylactic treatment support a difference in response of predominantly manic bipolar conditions (BP-I and MDI patterns) from those that present mainly with depression (BP-II). The former respond to lithium and to certain antipsychotics, and the subsequent depressive phases may also be reduced by lamotrigine. Lithium is less effective in preventing depression but combined treatment with selective serotonin reuptake inhibitors (SSRIs) plus lithium or an atypical antipsychotic may be effective. Quetiapine improves anxiety that is co-morbid with bipolar depression. Large observational studies indicate different patterns of response in co-morbid substance misuse. Rapid-cycling BP-I may respond to an antipsychotic; rapid-cycling BP-II sometimes benefits from lamotrigine.

Wednesday, April 6, 2005

S-67. Symposium: Influence of neurobiological factors on the course of depressive disorders

Chairperson(s): Matthias Rothermundt (Münster, Germany), Detlef E. Dietrich (Hannover, Germany)
08.30 - 10.00, Gasteig - Black Box

S-67-01

The influence of neuronal restructuring on the course of depressive disorders

M. Rothermundt, G. Ponath, G. Hetzel, D. E. Dietrich, V. Arolt. *University of Muenster Dept. Psychiatry, Münster, Germany*

Objective: Recent evidence suggests that neurodegenerative mechanisms may be involved in the pathophysiology of major depression. Structural and functional changes might be caused by alterations of dendrites and synapses. The astroglial protein S100B regulates the balance between proliferation and differentiation in neurons and glial cells affecting protective and apoptotic mechanisms. Two earlier studies reported increased S100B CSF and serum levels in acutely depressed patients.

Results: In study 1 the mean S100B serum concentration (immunofluorimetric sandwich assay) was significantly increased in depressed patients compared to healthy controls. The relative response rate to antidepressant therapy after 4 weeks correlated positively with S100B levels. In a regression analysis, only S100B concentrations and HAMD total score predicted the therapeutic response. In study 2 patients with increased S100B concentrations in the acute state showed a normalization of the initially extended P2- and P3-latencies in remission. In patients with unchanged S100B levels, however, the increased latencies remained elevated even in a remitted state. In study 3 patients with recurrent major depression were investigated in the state of clinical remission. Those patients with increased S100B concentrations in a remitted state demonstrated normalized N2- and P3-amplitudes while patients with lower S100B levels displayed pathologically decreased N2- and P3-amplitudes.

Conclusion: These findings suggest that alterations in dendrites and synapses might be involved in the pathogenesis of depression. S100B may be a parameter indicating neuronal restructuring.

S-67-02

The HPA system in depression: Indicator of vulnerability and treatment response

https://doi.org/10.1016/S0924-9338(05)80069-0 Published online by Cambridge University Press

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Dysregulation of the HPA system is one of the most replicated neuroendocrine findings in depression. As shown in several studies, using the combined dexamethasone/Corticotropin Releasing Hormone (Dex/CRH) test, the HPA hyperactivity gradually normalizes during successful antidepressant treatment. Usually the normalization of the HPA system precedes the clinical remission. A persistent HPA dysregulation in spite of remission of clinical symptoms predicts a high risk for relapse. Thus, there is a close association between HPA regulation and depression, which also suggests a causal relationship. While the relationship between the global severity of the depression and the HPA activity is only weak, the normalisation of the HPA function during the treatment is strongly correlated with improvement of specific cerebral functions: there is a strong correlation between improvement of working memory function and reduction of the cortisol secretio. But HPA alterations also occur in healthy first degree relatives of depressed patients, which points to an increased vulnerability. Other vulnerability factors for depression are high scores in personality and temperament dimensions as neuroticism and depressive temperament. In a sample of healthy volunteers a correlation between neuroticism and depressive temperament on the one hand and HPA activity on the other could be shown. These findings point to a causal relationship of HPA dysregulation on the pathophysiology of depression and give reason to the development of treatment strategies, which aim directly to the restoration of the HPA integrity. One approach is the blockade of CRH1-receptors. In a first pilot study in 20 patients depressive symptomatology could markedly be reduced by application of a synthetic CRH1-receptor antagonist. Overall a large body of evidence supports the hypothesis that HPA dysregulation plays a crucial role in the development and maintenance of depression and opens new perspectives for treatment options.

S-67-03

Influence of Borna disease virus infection on the course of depression

D. E. Dietrich, H. M. Emrich. *Dept. Clinical Psychiatry, Han, Hannover, Germany*

Objective: Borna disease virus (BDV), a spheric, enveloped, negative- and single-stranded RNA virus with a diameter of 90nm, is supposed to be spread worldwide and was detected in several naturally infected mammals. Meanwhile studies report that BDV has been found in human beings showing a high prevalence especially in patients suffering from neuropsychiatric diseases such as bipolar and recurrent depressive disorders (Bode et al. 2001). Therefore, BDV was hypothesized to represent an etiopathogenetic factor in these disorders. Experimental findings in animals showed a virus persistence especially in limbic structures and an alternation between active and latent viral infection. Moreover, it was demonstrated that BDV interacts with aspartate- and glutamate receptors in the hippocampal formation. The pathomechanism in infected humans is still unknown, but results of epidemiological studies suggest a possible impact of BDV on depressive disorders.

Methods: In our clinic we investigated the effect of the antiviral compound amantadine-sulphate on BDV parameters and symptoms in BDV-infected depressive patients in an open trial (n=25) as well as in a double-blind and placebo-controlled study (n=33). Furthermore, event-related brain potentials were used to investigate cognitive processing in BDV-infected and depressed patients with an obsessive-compulsive disorder (OCD).

Results: It appears that certain subtypes of affective disorders show a better response rate to the amantadine-treatment than others. In addition, the clinical improvement was paralleled by a reduction of BDV-infection parameters. Moreover, BDV also appeared to be correlated to certain changes of cognitive functions independent from depressive symptoms in OCD.

Conclusion: We will discuss these findings based on a model of the influence of BDV in neuropsychiatric diseases, suggesting that BDV-infection is a possible factor influencing the course of certain subtypes of depressive disorders.

S-67-04

J. Joost. *Netherlands*

S-67-05

Hippocampal changes and white matter lesions in early-onset depression

J. Janssen, H. Hulshoff Pol, I. Lamp, H. Schnack, F. E. de leeuw, R. Kahn, T. Heeren. *Utrecht University Medical Center, Utrecht, Netherlands*

Objective: Hippocampal volume reduction and increased prevalence of subcortical white matter lesions have been reported in late-life depression. We aimed to examine whether total number of subcortical white matter lesions were associated with reduced hippocampal volume in aged female subjects with early-onset depression (<45 years) and healthy comparison subjects.

Methods: The study included 28 middle aged and elderly subjects with major depression and 41 age-matched control subjects. Hippocampal, parahippocampal gyrus, and orbitofrontal cortex volumes were determined using manual tracing methods. White matter lesions were rated from T2-weighted MRI scans using a semi-quantitative classification scale.

Results: After controlling for total brain volume and age, patients had reduced hippocampal volume due to right hippocampal volume decrease (2.84 ml versus 3.12 ml, $F=16.6$, $p<.001$). Parahippocampal and orbitofrontal volumes did not differ significantly between groups. Multiple linear regression analysis indicated that reduced hippocampal volume did not significantly correlate with total number of subcortical white matter lesions ($t=.673$, $p=.518$).

Conclusion: Right hippocampal volume was reduced in aged female early-onset depressed subjects. Total number of subcortical white matter lesions was not associated with the decrease in right hippocampal volume. Our data suggests hippocampal involvement, independent of subcortical white matter lesions, in the neuropathology of early-onset depression.

Monday, April 4, 2005

SS-10. Section symposium: Mood disorders and somatic syndromes

Chairperson(s): Martin Preisig (Prilly, Switzerland), Jules Angst (Zürich, Switzerland)
16.15 - 17.45, Gasteig - Lecture Hall Library

https://doi.org/10.1016/S0924-9338(05)80069-0 Published online by Cambridge University Press