



Is Depression a Risk Factor of Worse Response to Therapy in Epilepsy?

Neuropsychiatric Symptomatology Predicts Seizure Recurrence in Newly Treated Patients.

Petrovski S, Szoecke CEI, Jones NC, Salzberg LJ, Sheffield RM, Huggins RM, O'Brien TJ. *Neurology*, 2010;75:1015–1021.

OBJECTIVES: To test the hypothesis that neuropsychiatric symptomatology is predictive of the success of seizure control in patients newly treated with antiepileptic drugs (AEDs), and that this predictive value adds to that provided by other clinical, imaging, and genomic factors in a multivariate model. **METHODS:** One hundred seventy newly treated patients with epilepsy completed the A-B Neuropsychological Assessment Scale (ABNAS) before commencing AED therapy and were prospectively followed up for 12 months. Patients were classified as nonresponsive if they had at least 1 seizure not explained by medication noncompliance or other significant provoking factors. **RESULTS:** Of the 138 patients in whom a drug response phenotype at 12 months was able to be determined, nonresponsive patients ($n = 45$) had a higher pretreatment ABNAS score than patients whose seizures were controlled ($n = 93$) ($p = 0.007$). A lesion on MRI was also associated with a higher risk of seizure recurrence ($p = 0.003$). On multivariate logistic regression, the ABNAS score, the MRI results, and a genomic classifier were all independently predictive of treatment outcome. For AED pharmacoresponse, this multivariate model had diagnostic values of 91% sensitivity, 64% specificity, 84% positive predictive, and 78% negative predictive values. The predictive value of the ABNAS score was validated in a second prospective cohort of 74 newly treated patients with epilepsy ($p = 0.005$). **CONCLUSIONS:** The ABNAS provides prognostic information regarding successful seizure control in patients newly treated with AEDs. Furthermore, these results demonstrate the multifactorial nature of the determinants of AED response, with neuropsychological, structural, and genomic factors all contributing to the complex response phenotype.

Commentary

Depressive disorders (DD) are common psychiatric comorbidities of epilepsy, stroke, Parkinson's disease, multiple sclerosis, and dementia. While they are often considered to be a complication of these neurologic disorders, epidemiologic studies published in the last 15 years have suggested a bidirectional relation. Indeed, not only are these neurologic conditions associated with an increased risk of DD, but a history of depression has been associated with a four- to seven-fold higher risk of developing epilepsy (1) and a two- to three-fold higher risk of having a stroke, Parkinson's disease, or dementia (2–4). This bidirectional relation does not imply causality but reflects most likely the presence of common pathogenic mechanisms operant in DD and these neurologic disorders.

In epilepsy, a history of DD has been also associated with a higher risk of pharmaco-resistance to antiepileptic drugs (AEDs). For example, in a study of 780 patients with new onset epilepsy, Hitiris et al. (5) found that individuals with a history of psychiatric disorders, and particularly depression, were two-fold less likely to be seizure-free with AED after a median

follow-up period of 79 months compared with patients without a psychiatric history. Likewise, in a study of 138 patients with new onset epilepsy (the study by Petrovski et al. selected for this commentary), those with symptoms of depression and anxiety at the time of diagnosis of epilepsy were significantly less likely to be seizure-free at the 1-year follow-up evaluation.

The negative impact of DD on response to therapy has been observed not only in pharmacotherapy but also in patients undergoing epilepsy surgery. For example, in a study of 100 consecutive patients with treatment-resistant temporal lobe epilepsy (TLE) who had an anterior temporal lobectomy, Kanner et al. (6) found that patients with a lifetime history of depression were 19-fold less likely to be free of auras and 7-fold less likely to be free of disabling seizures than patients without a psychiatric history. Likewise, in a study of 121 patients who underwent a temporal lobectomy, Anhoury et al. (7) found a significant association between a presurgical psychiatric history and a worse postsurgical seizure outcome.

How can these data be explained? While no definite answer is available at this time, some have questioned whether worse seizure control is related to poor compliance with AEDs or the misdiagnosis of psychogenic non-epileptic seizures as epileptic seizures. This possibility was ruled out, however, in some of the studies cited above (6). Recent neuroimaging studies may provide some answers. For example, in a study of



48 adults with treatment-resistant TLE, Barioni Salgado et al. compared voxel-based morphometric analyses of brain MRI studies among patients with DD ($n = 24$), patients without DD ($n = 24$), and a healthy control group ($n = 86$) (8). Patients with TLE with DD displayed a higher number of areas of gray matter volume loss than those with without depression in temporal and frontal lobe regions bilaterally and in the left thalamus. Of note, in a separate study of 165 patients with TLE, the same group of investigators found that gray matter atrophy in patients with treatment-resistant and remitting-relapsing epilepsy was more widespread than in seizure-free patients (9). Significant differences included cortical atrophy of bilateral periorbital cortex, cingulum, and temporal lobes.

Atrophy of mesial-temporal and frontal lobe structures have been also documented in volumetric studies of patients with primary major DD. Furthermore, neuropathologic studies performed in brains of patients with primary major DD have revealed decreases in cortical thickness, neuronal sizes, and neuronal and glial densities in several cortical layers of the orbitofrontal and dorsolateral frontal cortex. Also, recent data suggest that hippocampal atrophy may in fact precede the onset of primary DD. Indeed, Chen et al. performed voxel-based morphometry analyses in brain MRI studies of 55 asymptomatic adolescent girls: 23 were considered to be at high risk for depression, as their mothers experienced recurrent episodes of depression, while the mothers of the other 32 age-matched girls (controls) had no history of psychopathology (low-risk) (10). Significantly less gray matter density was found in both hippocampi of the girls at high-risk girls for DD, than in those of the control group. The existence of other potential common pathogenic mechanisms operant in DD and epilepsy have been suggested, including disturbances of neurotransmitters such as serotonin, norepinephrine, and glutamate as well as a hyperactive hypothalamic–pituitary–adrenal axis, all of which have been found to facilitate cortical hyperexcitability and faster kindling in animal models of epilepsy; these data have been reviewed elsewhere (11).

The negative effect of DD on the course of the other major neurologic disorders has also been reported. For example, the development of post-stroke depression has been associated with a worse recovery of both cognitive functions and the ability to perform activities of daily living, as well as a higher mortality risk (12). Likewise, the presence of depression in patients with Parkinson's disease has been associated with a more rapid deterioration of motor and cognitive functions, especially executive function, and a greater likelihood of displaying psychotic symptoms and physical disability. In the case of dementia, DD have been associated with greater impairment in activities of daily living and were found to be a predictor of cognitive decline leading to an earlier need for placement in a nursing home and discharge from an assisted-living facility to a higher level facility.

In conclusion, the presence of bilateral hippocampal atrophy, diffuse cortical atrophy, or both in those with a history of DD at the time of onset of epilepsy may provide a possible

explanation for the worse pharmacologic treatment response to AEDs. This hypothesis may also be applicable for the worse course of the other neurologic disorders in the presence of DD. Whether or not a timely treatment of DD would prevent these potential negative effects on these neurologic disorders has yet to be investigated. Clearly, these data highlight the need for early identification of family history and comorbid DD in patients with neurologic disorders. In addition, it is time that DD be included as a covariate in the analyses of studies investigating pharmacologic and surgical treatment strategies of these conditions. And by the way... if a bidirectional relation between depression and most major neurologic disorders appears to be clear, isn't it time that a bidirectional interaction start taking place between neurologists and psychiatrists?

By Andres M. Kanner, MD

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