Update 1 - Dec 2013

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UPDATE

Abstract-1
De novo Huntington disease caused by 26-44 CAG repeat expansion on a low-risk haplotype.

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Neurology. 2013 Sep 17;81(12):1099-100. doi: 10.1212/WNL.0b013e3182a4a4af. Epub 2013 Aug 14.

Abstract

Huntington disease (HD, OMIM #143100) is a dominantly inherited neurodegenerative disorder due to a CAG repeat expansion in the HTT gene, encoding a polyglutamine tract in the N-terminal part of the huntingtin protein. Most cases are inherited from an affected parent, but in about 10% of cases the condition appears to be de novo. De novo or sporadic cases are usually due to CAG repeat expansion of intermediate alleles. Intermediate alleles have 27-35 CAG repeats, and the higher the number of repeats, the higher the risk for expansion into disease range, usually upon paternal transmission. In most cases, the change in repeat size is minor, and gradual increases into the disease range over several generations is the basis of new genetic mutations and stable disease prevalence. So far, the largest single-step expansions reported were from 27 to 38 and from 35 to 58 CAG repeats. It has recently been shown that intermediate alleles and disease alleles share the same haplotypes, which is expected if intermediate alleles are the main source of new mutation cases. The high-risk haplotypes are called A1 and A2, and are both prevalent among Caucasians but rare in other ethnic groups.

Abstract-2
Late-onset anti-NMDA receptor encephalitis.

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Abstract

OBJECTIVE: To describe the clinical features and outcome of antiNMDA receptor (NMDAR) encephalitis in patients ≥ 45 years old.

METHODS: Observational cohort study.

RESULTS: In a cohort of 661 patients with anti-NMDAR encephalitis, we identified 31 patients ≥ 45 years old. Compared with younger adults (18-44 years), older patients were more often male (45% vs 12%, $p < 0.0001$), had lower frequency of tumors (23% vs 51%, $p = 0.002$; rarely teratomas), had longer median time to diagnosis (8 vs 4 weeks, $p = 0.009$) and treatment (7 vs 4 weeks, $p = 0.039$), and had less favorable outcome (modified Rankin Scale score 0-2 at 2 years, 60% vs 80%, $p < 0.026$). In multivariable analysis, younger age (odds ratio [OR] 0.15, confidence interval [CI] 0.05-0.39, $p = 0.0001$), early treatment (OR 0.60, CI 0.47-0.78, $p < 0.0001$), no need for intensive care (OR 0.09, CI 0.04-0.22, $p < 0.0001$), and longer follow-up ($p < 0.0001$) were associated with good outcome. Rituximab and cyclophosphamide were effective when first-line immunotherapies failed (OR 2.93, CI 1.10-7.76, $p = 0.031$). Overall, 60% of patients older than 45 years had full or substantial recovery at 24 months follow-up.

CONCLUSION: Anti-NMDAR encephalitis is less severe in patients ≥ 45 years old than in young adults, but the outcome is poorer in older patients. In this age group, delays in diagnosis and treatment are more frequent than in younger patients. The frequency of underlying tumors is low, but if present they are usually carcinomas instead of teratomas in younger patients. Early and aggressive immunotherapy will likely improve the clinical outcome.

Abstract-3

Encephalitis and GABAB receptor antibodies: Novel findings in a new case series of 20 patients.

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Neurology. 2013 Oct 22;81(17):1500-6. doi: 10.1212/WNL.0b013e3182a9585f. Epub 2013 Sep 25.

Abstract

OBJECTIVE: To report the clinical features of 20 newly diagnosed patients with GABAB receptor (GABABR) antibodies and determine the frequency of associated tumors and concurrent neuronal autoantibodies.

METHODS: Clinical data were retrospectively obtained and evaluated. Serum and CSF samples were examined for additional antibodies using methods previously reported.

RESULTS: Seventeen patients presented with seizures, memory loss, and confusion, compatible with limbic encephalitis (LE), one patient presented with ataxia, one patient presented with status epilepticus, and one patient presented with opsoclonus-myoclonus syndrome (OMS). Nineteen (95%) patients eventually developed LE during the course of the disease. Small-cell lung cancer (SCLC) was identified in 10 (50%) patients, all with LE. Treatment and outcome was available from 19 patients: 15 showed complete (n = 7) or partial (n = 8) neurologic improvement after steroids, IV immunoglobulins, or plasma exchange and oncologic treatment when indicated; 1 patient died of tumor progression shortly after the first cycle of immunotherapy, and 3 were not treated. Five patients with SCLC had additional onconeuronal antibodies (Ri, amphiphysin, or SOX1), and 2 without tumor had GAD65 and NMDAR antibodies, respectively. GABABR antibodies were not detected in serum of 116 patients with SCLC without neurologic symptoms.

CONCLUSION: Our study confirms GABABR as an autoantigen of paraneoplastic and nonparaneoplastic LE and expands the phenotype of GABABR antibodies to ataxia, OMS, and status epilepticus. The long-term prognosis is dictated by the presence of a tumor. Recognition of syndromes associated with GABABR antibodies is important because they usually respond to treatment.

Abstract-4

Herpes simplex virus1 encephalitis can trigger anti-NMDA receptor encephalitis: Case report.

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Neurology. 2013 Oct 29;81(18):1637-9. doi: 10.1212/WNL.0b013e3182a9f531. Epub 2013 Oct 2.

Abstract

Relapsing symptoms post herpes simplex virus 1 (HSV) encephalitis (HSVE) usually occur a few weeks after viral therapy and represent either 1) a true viral relapse of HSVE (CSF PCR positive for HSV, new necrotic lesions on brain MRI, and response to acyclovir therapy) or 2) a disorder postulated to be immune-mediated (CSF negative for HSV, no new necrotic lesions, and no response to acyclovir). It has been suggested that this immune-mediated disorder may be related to NMDA receptor (NMDAR) antibodies, and we recently reported a child in whom relapsing symptoms post HSVE were the presentation of anti-NMDAR encephalitis. We report an adult with this disorder, demonstrate that synthesis of NMDAR antibodies began after HSVE, and show that relapsing symptoms were due to steroid-responsive anti-NMDAR encephalitis.

Abstract-5
B-type natriuretic peptides and mortality after stroke-A systematic review and meta-analysis.

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Abstract

OBJECTIVE: To measure the association of B-type natriuretic peptide (BNP) and N-terminal fragment of BNP (NT-proBNP) with all-cause mortality after stroke, and to evaluate the additional predictive value of BNP/NT-proBNP over clinical information.

METHODS: Suitable studies for meta-analysis were found by searching MEDLINE and EMBASE databases until October 26, 2012. Weighted mean differences measured effect size; meta-regression and publication bias were assessed. Individual participant data were used to estimate effects by logistic regression and to evaluate BNP/NT-proBNP additional predictive value by area under the receiver operating characteristic curves, and integrated discrimination improvement and categorical net reclassification improvement indexes.

RESULTS: Literature-based meta-analysis included 3,498 stroke patients from 16 studies and revealed that BNP/NT-proBNP levels were 255.78 pg/mL (95% confidence interval [CI] 105.10-406.47, p = 0.001) higher in patients who died; publication bias entailed the loss of this association. Individual participant data analysis comprised 2,258 stroke patients. After normalization of the data, patients in the highest quartile had double the risk of death after adjustment for clinical variables (NIH Stroke Scale score, age, sex) (odds ratio 2.30, 95% CI 1.32-4.01 for BNP; and odds ratio 2.63, 95% CI 1.75-3.94 for NT-proBNP). Only NT-proBNP showed a slight added value to clinical prognostic variables, increasing discrimination by 0.028 points (integrated discrimination improvement index; p < 0.001) and reclassifying 8.1% of patients into correct risk mortality categories (net reclassification improvement index; p = 0.003). Neither etiology nor time from onset to death affected the association of BNP/NT-proBNP with mortality.

CONCLUSION: BNPs are associated with poststroke mortality independent of NIH Stroke Scale score, age, and sex. However, their translation to clinical practice seems difficult because BNP/NT-proBNP add only minor predictive value to clinical information.

Abstract-6
Predicting stroke mortality-BNP could it be?

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Abstract

Physicians, patients, and families rely on clinical factors associated with stroke mortality to guide decisions of care and set goals of medical therapy. However, these factors, including age and baseline neurologic impairment, are at best imperfect predictors and additional prognostic tools are needed. Biomarkers such as B-type natriuretic peptide (BNP) have potential. However, for a biomarker to be of clinical utility, it needs to add information beyond what clinical predictors can provide. BNP is produced by myocardial tissue in response to strain and acts to reduce systolic blood pressure through vasodilation and natriuresis. In stroke, BNP has been associated with increased mortality.

Abstract-7
Predictors of outcome in acute encephalitis

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Neurology. 2013 Aug 27;81(9):793-800. doi: 10.1212/WNL.0b013e3182a2cc6d. Epub 2013 Jul 26.

Abstract

OBJECTIVE: To investigate predictors of outcome in patients with all-cause encephalitis receiving care in the intensive care unit.

METHODS: A retrospective analysis of encephalitis cases at The Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center was performed. Using multivariate logistic regression analysis, we examined mortality and predictors of good outcome (defined as modified Rankin Scale scores of 13) and poor outcome (scores 4 and 5) in those surviving to hospital discharge.

RESULTS: In our cohort of 103 patients, the median age was 52 years (interquartile range 26), 52 patients (50.49%) were male, 28 patients (27.18%) had viral encephalitis, 19 (18.45%) developed status epilepticus (SE), 15 (14.56%) had cerebral edema, and 19 (18.45%) died. In our multivariate logistic regression analysis, death was associated with cerebral edema (odds ratio [OR] 18.06, 95% confidence interval [CI] 3.14-103.92), SE (OR 8.16, 95% CI 1.55-43.10), and thrombocytopenia (OR 6.28, 95% CI 1.41-28.03). Endotracheal intubation requirement with ventilator support was highly correlated with death (95%). In addition, in those patients who survived, viral, nonviral, and unknown causes of encephalitis were less likely to have a poor outcome at hospital discharge compared with an autoimmune etiology (viral encephalitis: OR 0.09, 95% CI 0.01-0.57; nonviral encephalitis: OR 0.02, 95% CI 0.01-0.31; unknown etiology: OR 0.18, 95% CI 0.04-0.91).

CONCLUSION: Our study suggests that predictors of death in patients with encephalitis comprise potentially reversible conditions including cerebral edema, SE, and thrombocytopenia. Further prospective studies are needed to determine whether aggressive management of these complications in patients with encephalitis improves outcome.

Abstract-8
Unrecognized vitamin D3 deficiency is common in Parkinson disease-Harvard Biomarker Study

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Lewis R. Sudarsky, MD, John H. Growdon, MD and Clemens R. Scherzer, MD

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Abstract

OBJECTIVE: To conclusively test for a specific association between the biological marker 25-hydroxy-vitamin D3, a transcriptionally active hormone produced in human skin and liver, and the prevalence and severity of Parkinson disease (PD).

METHODS: We used liquid chromatography/tandem mass spectrometry to establish an association specifically between deficiency of 25-hydroxy-vitamin D3 and PD in a cross-sectional and longitudinal case-control study of 388 patients (mean Hoehn and Yahr stage of 2.1 ± 0.6) and 283 control subjects free of neurologic disease nested in the Harvard Biomarker Study.

RESULTS: Plasma levels of 25-hydroxy-vitamin D3 were associated with PD in both univariate and multivariate analyses with p values = 0.0034 and 0.047, respectively. Total 25-hydroxy-vitamin D levels, the traditional composite measure of endogenous and exogenous vitamin D, were deficient in 17.6% of patients with PD compared with 9.3% of controls. Low 25-hydroxy-vitamin D3 as well as total 25-hydroxy-vitamin D levels were correlated with higher total Unified Parkinson's Disease Rating Scale scores at baseline and during follow-up.

CONCLUSION: Our study reveals an association between 25-hydroxy-vitamin D3 and PD and suggests that thousands of patients with PD in North America alone may be vitamin Ddeficient. This finding has immediate relevance for individual patients at risk of falls as well as public health, and warrants further investigation into the mechanism underlying this association.