Update 2 - Jan 2014

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Neuro Diagnostic Excellence
UPDATE

Abstract-1
Updated estimate of AQP4-IgG serostatus and disability outcome in neuromyelitis optica.

Jiao Y, Fryer JP, Lennon VA, Jenkins SM, Quek AM, Smith CY, McKeon A, Costanzi C, Iorio R, Weinshenker BG, Wingerchuk DM, Shuster EA,Lucchinetti CF, Pittock SJ

Neurology. 2013 Oct 1;81(14):1197-204. doi: 10.1212/WNL.0b013e3182a6cb5c. Epub 2013 Aug 30.

Abstract

OBJECTIVE: To 1) determine, using contemporary recombinant antigenbased assays, the aquaporin-4 (AQP4)-immunoglobulin G (IgG) detection rate in sequential sera of patients assigned a clinical diagnosis of neuromyelitis optica (NMO) but initially scored negative by tissue-based indirect immunofluorescence (IIF) assay; and 2) evaluate the impact of serostatus on phenotype and outcome.

METHODS: From Mayo Clinic records (2005-2011), we identified 163 patients with NMO; 110 (67%) were seropositive by IIF and 53 (33%) were scored seronegative. Available stored sera from 49 "seronegative" patients were tested by ELISA, AQP4-transfected cell-based assay, and in-house fluorescence-activated cell sorting assay. Clinical characteristics were compared based on final serostatus.

RESULTS: Thirty of the 49 IIF-negative patients (61%) were reclassified as seropositive, yielding an overall AQP4-IgG seropositivity rate of 88% (i.e., 12% seronegative). The fluorescence-activated cell sorting assay improved the detection rate to 87%, cell-based assay to 84%, and ELISA to 79%. The sex ratio (female to male) was 1:1 for seronegatives and 9:1 for seropositives ($p < 0.0001$). Simultaneous optic neuritis and transverse myelitis as onset attack type (i.e., within 30 days of each other) occurred in 32% of seronegatives and in 3.6% of seropositives ($p < 0.0001$). Relapse rate, disability outcome, and other clinical characteristics did not differ significantly.

CONCLUSION: Serological tests using recombinant AQP4 antigen are significantly more sensitive than tissue-based IIF for detecting AQP4-IgG. Testing should precede immunotherapy; if negative, later-drawn specimens should be tested. AQP4-IgGseronegative NMO is less frequent than previously reported and is clinically similar to AQP4-IgGseropositive NMO.

Abstract - 2
RAS-MAPK-MSK1 pathway modulates ataxin 1 protein levels and toxicity in SCA1.

Park J, Al-Ramahi I, Tan Q, Mollema N, Diaz-Garcia JR, Gallego-Flores T, Lu HC, Lagalwar S, Duvick L, Kang H, Lee Y, Jafar-Nejad P, Sayegh LS,Richman R, Liu X, Gao Y, Shaw CA, Arthur JS, Orr HT, Westbrook TF, Botas J, Zoghbi HY

Nature. 2013 Jun 20;498(7454):325-31. doi: 10.1038/nature12204. Epub 2013 May 29.

Abstract

Many neurodegenerative disorders, such as Alzheimer's, Parkinson's and polyglutamine diseases, share a common pathogenic mechanism: the abnormal accumulation of disease-causing proteins, due to either the mutant protein's resistance to degradation or overexpression of the wild-type protein. We have developed a strategy to identify therapeutic entry points for such neurodegenerative disorders by screening for genetic networks that influence the levels of disease-driving proteins. We applied this approach, which integrates parallel cell-based and Drosophila genetic screens, to spinocerebellar ataxia type 1 (SCA1), a disease caused by expansion of a polyglutamine tract in ataxin 1 (ATXN1). Our approach revealed that downregulation of several components of the RAS-MAPK-MSK1 pathway decreases ATXN1 levels and suppresses neurodegeneration in Drosophila and mice. Importantly, pharmacological inhibitors of components of this pathway also decrease ATXN1 levels, suggesting that these components represent new therapeutic targets in mitigating SCA1. Collectively, these data reveal new therapeutic entry points for SCA1 and provide a proof-of-principle for tackling other classes of intractable neurodegenerative diseases.

Abstract - 3
Natriuretic peptides as predictive biomarkers of stroke outcome.

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Neurology. 2013 Dec 3;81(23):1983. doi: 10.1212/01.wnl.0000436941.55281.9c. Epub 2013 Nov 1.

Abstract

B-type natriuretic peptide (BNP), along with an inactive N-terminal peptide fragment (NT-proBNP), is secreted by cardiac ventricular myocytes in response to excessive myocardial stretching. The plasma half-life of these peptides is 0.3 and 2.0 hours, respectively, so a single measurement mostly reflects recent cardiac stress that may for example reflect sympathetic stimulation in response to acute stroke. Results from a variety of clinical studies indicate that these peptides may be useful as biomarkers for a variety of both cardiac and cerebrovascular events. In a carefully performed meta-analysis, García-Berrocoso and colleagues evaluate the relationship of BNP and NT-proBNP levels with mortality following acute stroke. Although individuals in the highest quartile for either of the 2 peptides had twice the risk of death compared to the lower quartiles, only the NT-proBNP measures added slightly (additional 8.1% of patients) to the typical clinical measures for predicting stroke mortality including age, sex, and NIH Stroke Scale score. The results do not go far enough to establish a relationship between the cause of death and the highest natriuretic levels. Some suggestive data from the ARISTOTLE trial indicate that cardiac death has an important role but more careful studies that focus on the usefulness of measuring BNP or NT-proBNP within the first 24 hours after acute stroke, along with an analysis of the explicit causes of death, are needed.

Abstract - 4
Epstein-Barr virus in oral shedding of children with multiple sclerosis.

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Neurology. 2013 Oct 15;81(16):1392-9. doi: 10.1212/WNL.0b013e3182a841e4. Epub 2013 Sep 6.

Abstract

OBJECTIVE: To investigate Epstein-Barr virus (EBV) oral shedding frequency and EBV genetic diversity in pediatric patients with multiple sclerosis (MS).

METHODS: This was a prospective case-control study. We used PCR-based assays to detect viral DNA in the monthly mouth swabs of 22 pediatric patients with MS and 77 age- and sex-matched healthy controls. EBV-positive samples were further analyzed for sequence variation in the EBV BCRF1 (ebvIL-10) gene using direct DNA sequencing methods, and in the EBV LMP1 gene by mass spectrometry.

RESULTS: Nineteen of the 22 (86.4%) children with MS were seropositive for remote EBV infection compared to 35 out of 77 (45.5%) healthy controls ($p = 0.008$). Baseline analysis of mouth swabs revealed a higher proportion of EBV-positive samples from EBV-seropositive patients with MS compared to EBV-seropositive healthy controls (52.6% vs 20%, $p = 0.007$). Longitudinal analysis of monthly swabs revealed average EBV detection rates of 50.6% in patients with MS and 20.4% in controls ($p = 0.01$). The oral shedding frequencies of Herpesvirusesherpes simplex virus1, cytomegalovirus, human herpesvirus (HHV)-6, and HHV-7 did not differ between groups. Changes in the predominant EBV genetic variants were detected more frequently in patients with MS; however, no specific EBV genetic variant was preferentially associated with MS.

CONCLUSION: Children with MS demonstrate abnormally increased rates of EBV viral reactivation and a broader range of genetic variants, suggesting a selective impairment in their immunologic control of EBV.

Abstract - 5
Criteria for the diagnosis of corticobasal degeneration.

Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, Boxer AL, Dickson DW, Grossman M, Hallett M, Josephs KA, Kertesz A, Lee SE, Miller BL, Reich SG, Riley DE, Tolosa E, Tröster AI, Vidailhet M, Weiner WJ

Neurology. 2013 Jan 29;80(5):496-503. doi: 10.1212/WNL.0b013e31827f0fd1.

Abstract

Current criteria for the clinical diagnosis of pathologically confirmed corticobasal degeneration (CBD) no longer reflect the expanding understanding of this disease and its clinicopathologic correlations. An international consortium of behavioral neurology, neuropsychology, and movement disorders specialists developed new criteria based on consensus and a systematic literature review. Clinical diagnoses (early or late) were identified for 267 nonoverlapping pathologically confirmed CBD cases from published reports and brain banks. Combined with consensus, 4 CBD phenotypes emerged: corticobasal syndrome (CBS), frontal behavioral-spatial syndrome (FBS), nonfluent/agrammatic variant of primary progressive aphasia (naPPA), and progressive supranuclear palsy syndrome (PSPS). Clinical features of CBD cases were extracted from descriptions of 209 brain bank and published patients, providing a comprehensive description of CBD and correcting common misconceptions. Clinical CBD phenotypes and features were combined to create 2 sets of criteria: more specific clinical research criteria for probable CBD and broader criteria for possible CBD that are more inclusive but have a higher chance to detect other tau-based pathologies. Probable CBD criteria require insidious onset and gradual progression for at least 1 year, age at onset $\geqslant$ 50 years, no similar family history or known tau mutations, and a clinical phenotype of probable CBS or either FBS or naPPA with at least 1 CBS feature. The possible CBD category uses similar criteria but has no restrictions on age or family history, allows tau mutations, permits less rigorous phenotype fulfillment, and includes a PSPS phenotype. Future validation and refinement of the proposed criteria are needed.

Abstract - 6
Vitamin B supplementation, homocysteine levels, and the risk of cerebrovascular disease: a meta-analysis.

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Neurology. 2013 Oct 8;81(15):1298-307. doi: 10.1212/WNL.0b013e3182a823cc. Epub 2013 Sep 18.

Abstract

OBJECTIVE: To perform a meta-analysis on the effect of lowering homocysteine levels via B vitamin supplementation on cerebrovascular disease risk.

METHODS: Using clinical trials published before August 2012 to assess stroke events, we used relative risks (RRs) with 95% confidence intervals (95% CIs) to measure the association between B vitamin supplementation and endpoint events using a fixed-effects model and x2 tests. We included 14 randomized controlled trials with 54,913 participants in this analysis.

RESULTS: We observed a reduction in overall stroke events resulting from reduction in homocysteine levels following B vitamin supplementation (RR 0.93; 95% CI 0.86–1.00; p = 0.04) but not in subgroups divided according to primary or secondary prevention measures, ischemic vs hemorrhagic stroke, or occurrence of fatal stroke. There were beneficial effects in reducing stroke events in subgroups with $\geqslant$ 3 years follow-up time, and without background of cereal folate fortification or chronic kidney disease (CKD). Some trials that included CKD patients reported decreased glomerular filtration rate with B vitamin supplementation. We conducted detailed subgroup analyses for cyanocobalamin (vitamin B12) but did not find a significant benefit regarding intervention dose of vitamin B12 or baseline blood B12 concentration. Stratified analysis for blood pressure and baseline participant medication use showed benefits with >130 mm Hg systolic blood pressure and lower antiplatelet drug use in reducing stroke risk.

CONCLUSION: B vitamin supplementation for homocysteine reduction significantly reduced stroke events, especially in subjects with certain characteristics who received appropriate intervention measures.

Abstract - 7
Effects of Bacille Calmette-Guerin after the first demyelinating event in the CNS.

Ristori G, Romano S, Cannoni S, Visconti A, Tinelli E, Mendozzi L, Cecconi P, Lanzillo R, Quarantelli M, Buttinelli C, Gasperini C, Frontoni M, Coarelli G,Caputo D, Bresciamorra V, Vanacore N, Pozzilli C, Salvetti M

Neurology. 2014 Jan 7;82(1):41-8. doi: 10.1212/01.wnl.0000438216.93319.ab. Epub 2013 Dec 4.

Abstract

OBJECTIVE: To evaluate Bacille Calmette-Guérin (BCG) effects after clinically isolated syndromes (CIS).

METHODS: In a double-blind, placebo-controlled trial, participants were randomly assigned to receive BCG or placebo and monitored monthly with brain MRI (6 scans). Both groups then entered a preplanned phase with IM interferon-□-1a for 12 months. From month 18 onward, the patients took the disease-modifying therapies (DMTs) that their neurologist considered indicated in an open-label extension phase lasting up to 60 months.

RESULTS: Of 82 randomized subjects, 73 completed the study (33 vaccinated and 40 placebo). During the initial 6 months, the number of cumulative lesions was significantly lower in vaccinated people. The relative risks were 0.541 (95% confidence interval [CI] 0.308-0.956; p = 0.03) for gadolinium-enhancing lesions (the primary endpoint), 0.364 (95% CI 0.207-0.639; p = 0.001) for new and enlarging T2-hyperintense lesions, and 0.149 (95% CI 0.046-0.416; p = 0.001) for new T1-hypointense lesions. The number of total T1-hypointense lesions was lower in the BCG group at months 6, 12, and 18: mean changes from baseline were -0.09 ± 0.72 vs 0.75 ± 1.81 (p = 0.01), 0.0 ± 0.83 vs 0.88 ± 2.21 (p = 0.08), and -0.21 ± 1.03 vs 1.00 ± 2.49 (p = 0.02). After 60 months, the cumulative probability of clinically definite multiple sclerosis was lower in the BCG + DMT arm (hazard ratio = 0.52, 95% CI 0.27-0.99; p < 0.05), and more vaccinated people remained DMT-free (odds ratio = 0.20, 95% CI 0.04-0.93; p = 0.04).

CONCLUSION: Early BCG may benefit CIS and affect its long-term course.

CLASSIFICATION OF EVIDENCE: BCG, as compared to placebo, was associated with significantly reduced development of gadolinium-enhancing lesions in people with CIS for a 6-month period before starting immunomodulating therapy (Class I evidence).

Abstract - 8
Predicting dementia in Parkinson disease by combining neurophysiologic and cognitive markers.

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Neurology. 2014 Jan 21;82(3):263-70. doi: 10.1212/WNL.0000000000000034. Epub 2013 Dec 18.

Abstract

OBJECTIVE: To assess the ability of neurophysiologic markers in conjunction with cognitive assessment to improve prediction of progression to dementia in Parkinson disease (PD).

METHODS: Baseline cognitive assessments and magnetoencephalographic recordings from 63 prospectively included PD patients without dementia were analyzed in relation to PD-related dementia (PDD) conversion over a 7-year period. We computed Cox proportional hazard models to assess the risk of converting to dementia conveyed by cognitive and neurophysiologic markers in individual as well as combined risk factor analyses.

RESULTS: Nineteen patients (30.2%) developed dementia. Baseline cognitive performance and neurophysiologic markers each individually predicted conversion to PDD. Of the cognitive test battery, performance on a posterior (pattern recognition memory score < median; hazard ratio (HR) 6.80; p = 0.001) and a fronto-executive (spatial span score < median; HR 4.41; p = 0.006) task most strongly predicted dementia conversion. Of the neurophysiologic markers, beta power < median was the strongest PDD predictor (HR 5.21; p = 0.004), followed by peak frequency < median (HR 3.97; p = 0.016) and theta power > median (HR 2.82; p = 0.037). In combination, baseline cognitive performance and neurophysiologic measures had even stronger predictive value, with the combination of impaired fronto-executive task performance and low beta power being associated with the highest dementia risk (both risk factors vs none: HR 27.3; p < 0.001).

CONCLUSION: Combining neurophysiologic markers with cognitive assessment can substantially improve dementia risk profiling in PD, providing potential benefits for clinical care as well as for the future development of therapeutic strategies.