LOYOLA MEDICINE
We also treat the human spirit.®

Top 10 Advances in Clinical Neurology

XXII World Congress of Neurology
Santiago, Chile
October 31 – November 5, 2015

José Biller, MD, FACP, FAAN, FANA, FAHA
Professor and Chairman
Department of Neurology
Loyola University Chicago
Stritch School of Medicine

Disclosures

LOYOLA MEDICINE

- Financial Disclosures
  - Editor Journal of Stroke and Cerebrovascular Diseases
  - Editor Frontiers in Neurology
  - Stroke Editorial Board Member Up-To-Date
- Unlabeled/Unapproved Uses Disclosure
  - Nothing to disclose

Top 10 Advances in Clinical Neurology

LOYOLA MEDICINE

1. Mechanical thrombectomy for acute ischemic stroke due to large artery (distal ICA/proximal [M1 segment] MCA) occlusion
2. Novel oral anticoagulants (NOACs) for primary and secondary stroke prevention in non-valvular atrial fibrillation
3. Carotid artery revascularization for stroke prevention
4. Advances in endovascular approaches to cerebral aneurysms
5. Advances in thrombophilias
6. Neuromyelitis Optica (NMO) Spectrum Disorders
7. Newer treatments for Multiple Sclerosis
8. New advances in epilepsy treatment options
9. Advances in Parkinson's disease
10. Biomarkers in neurodegenerative disorders

2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients with Acute Ischemic Stroke Regarding Endovascular Treatment

A Guideline for Healthcare Professionals from the American Heart Association, American Stroke Association

William J. Powers, MD, FAHA, Chair; Colin P. Derdeyn, MD, FAHA, Vice Chair; José Biller, MD, FAHA; Christopher S. Coffey, PhD; Brian L. Hoh, MD, FAHA; Edward C. Jauch, MD, MS, FAHA; Karen C. Johnston, MD, MSc; S. Claiborne Johnston, MD, PhD; Alexander A. Khalessi, MD, MS, FAHA; Chelsea S. Kidwell, MD, FAHA; James Meschia, MD, FAHA; Bruce Ovbiagele, MD, MSc, MAS; Dileep R. Yavagal, MD, MBBS on behalf of the American Heart Association Stroke Council

Stroke. Published online June 29, 2015

Stroke Neurologist's Perspective on the New Endovascular Trials

James C. Grotta, MD; Werner Hacke, MD

Abstract—Before December 2014, the only proven effective treatment for acute ischemic stroke was recombinant tissue-type plasminogen activator (r-tPA). This has now changed with the publication of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE), Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND IA), Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment Trial (SWIFT PRIME), and Randomized Trial of Revascularization With the Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset (REVASCAT) studies. We review the main results of these studies and how they inform stroke patient management going forward. The main take home points for neurologists are (1) intra-arterial thrombectomy is a potently effective treatment and should be offered to patients who have documented occlusion in the distal internal carotid or the proximal middle cerebral artery, have a relatively normal noncontrast head computed tomographic scan, severe neurological deficit, and can have intra-arterial thrombectomy within 6 hours of last seen normal; (2) benefits are clear in patients receiving r-tPA before intra-arterial thrombectomy; r-tPA should not be withheld if the patient meets criteria, and benefit in patients who do not receive r-tPA or have r-tPA exclusions requires further study; and (3) these favorable results occur when intra-arterial thrombectomy is performed in an endovascular stroke center by a coordinated multidisciplinary team that extends from the prehospital stage to the endovascular suite, minimizes time to recanalization, uses stent-retriever devices, and avoids general anesthesia. In conclusion, stroke teams, including practicing neurologists caring for patients with stroke should now provide the option for intra-arterial thrombectomy for a subset of patients with acute stroke. **(*Stroke*. 2015;46:1447-1452. DOI: 10.1161/STROKEAHA.115.008384.)**

Key Words: cerebral infarction ■ clinical trials, randomized ■ thrombolytic therapy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D., Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators*

Review Article

Journal of the Royal Society of Medicine Cardiovascular Disease
0(0) 1–8

DOI: 10.1177/2048004014529419
cvd.sagepub.com
SAGE

Asymptomatic carotid stenosis: What we can learn from the next generation of randomized clinical trials

Mark N Rubin, Kevin M Barrett, Thomas G Brott and James F Meschia

Abstract

Stroke remains an exceedingly incident and prevalent public health burden across the globe, with an estimated 16 million new strokes per annum and prevalence over 60 million, and extracranial internal carotid artery atherosclerotic disease is an important risk factor for stroke. Randomized trials of surgical treatment were conducted (North American Symptomatic Carotid Endarterectomy Trial, European Carotid Surgery Trial) and demonstrated efficacy of carotid endarterectomy for secondary prevention of stroke in patients with cerebrovascular events (e.g. ipsilateral stroke, transient ischemic attack, and/or amaurosis fugax) attributable to a diseased artery with 50–99% stenosis. Therapeutic clarity, however, proved elusive with asymptomatic carotid artery disease. Asymptomatic Carotid Atherosclerosis Study (ACAS), Asymptomatic Carotid Surgery Trial, and Veterans Affairs Cooperative Study (VACS) suggested only modest benefit from surgical intervention for primary stroke prevention and the best medical therapy at the time of these trials is not comparable to modern medical therapy. ACT-1, Asymptomatic Carotid Surgery Trial-2, Stent-Protected Angioplasty in asymptomatic Carotid artery stenosis versus Endarterectomy Trial-2, European Carotid Surgery Trial-2, Carotid Revascularization Endarterectomy Versus Stenting Trial-2 are trials that are recent, ongoing, or in development that include diverse populations across Europe and North America, complementary trial designs, and a collaborative spirit that should provide clinicians with evidence that informs best clinical practice for asymptomatic carotid artery disease.

Keywords

Carotid stenosis, primary and secondary stroke prevention, cardiology, carotid endarterectomy, angioplasty and stenting

Review

Cerebrovascular Diseases

Cerebrovasc Dis 2015;39:253–261
DOI: 10.1159/000381108

Received: January 21, 2015
Accepted: February 17, 2015
Published online: April 8, 2015

Moving Beyond Luminal Stenosis: Imaging Strategies for Stroke Prevention in Asymptomatic Carotid Stenosis

Ajay Gupta[a, b] Randolph S. Marshall[c]

[a]Department of Radiology, [b]Brain and Mind Research Institute, Weill Cornell Medical College, and [c]Department of Neurology, Columbia University Medical Center, New York, N.Y., USA

Key Words

Carotid stenosis · MRI · Ultrasound · Transcranial Doppler · Stroke

Abstract

Background: With progressive improvements in medical therapy and resultant reductions in stroke risk, luminal stenosis criteria are no longer adequate to inform decisions to pursue surgical revascularization in patients with asymptomatic carotid artery stenosis. ***Summary:*** In this evidence-based review, we discuss the imaging-based risk stratification strategies that take into account factors beyond luminal stenosis measurements, including cerebral hemodynamics and plaque composition. The existing literature lends support to the use of certain imaging tests in patients with asymptomatic carotid stenosis including cerebrovascular reserve testing, MRI of plaque composition, ultrasound of plaque echolucency, and transcranial Doppler evaluation for microemboli. The highest quality evidence thus far in the literature includes only systematic reviews and meta-analyses of cohort studies with no randomized trials having yet been performed to show how these newer imaging biomarkers could be used to inform treatment decisions in asymptomatic carotid stenosis. Beyond the need for randomized trials, there are additional important steps needed to improve the relevance of evidence supporting risk assessment strategies. Imaging studies evaluating the risk of stroke in carotid disease should clearly define asymptomatic versus symptomatic disease, use uniform definitions of clearly defined outcome measures such as ipsilateral stroke, ensure that imaging interpretations are performed in a manner blinded to treatments and other risk factors, and include cohorts which are on modern intensive medical therapy. Such studies of risk stratification for asymptomatic carotid stenosis will be most valuable if they can integrate multiple high-risk features (including clinical risk factors) into a multi-factorial risk assessment strategy in a manner that is relatively simple to implement and generalizable across a wide range of practice settings. ***Key Messages:*** Together, modern imaging strategies allow for a more mechanistic assessment of stroke risk in carotid disease compared to luminal stenosis measurements alone, which, with further validation in randomized controlled trials, may improve current efforts at stroke prevention in asymptomatic carotid stenosis.

Clinical Background

Various angiographic measurements of vessel narrowing have long played a central role in stroke risk stratification in patients with carotid artery stenosis, the cause of approximately 10–15% of all ischemic strokes [1]. Lu-

Absence of Microemboli on Transcranial Doppler Identifies Low-Risk Patients With Asymptomatic Carotid Stenosis

J. David Spence, MD; Arturo Tamayo, MD; Stephen P. Lownie, MD;
Wai P. Ng, MD; Gary G. Ferguson, MD, PhD

Background and Purpose—Carotid endarterectomy clearly benefits patients with symptomatic severe stenosis (SCS), but the risk of stroke is so low for asymptomatic patients (ACS) that the number needed to treat is very high. We studied transcranial Doppler (TCD) embolus detection as a method for identifying patients at higher risk who would have a lower number needed to treat.

Methods—Patients with carotid stenosis of ≥60% by Doppler ultrasound who had never been symptomatic (81%) or had been asymptomatic for at least 18 months (19%) were studied with TCD embolus detection for up to 1 hour on 2 occasions a week apart; patients were followed for 2 years.

Results—319 patients were studied, age (standard deviation) 69.68 (9.12) years; 32 (10%) had microemboli at baseline (TCD+). Events were more likely to occur in the first year. Patients with microemboli were much more likely to have microemboli 1 year later (34.4 versus 1.4%; $P<0.0001$) and were more likely to have a stroke during the first year of follow-up (15.6%, 95% CI, 4.1 to 79; versus 1%, 95% CI, 1.01 to 1.36; $P<0.0001$).

Conclusions—Our findings indicate that TCD− ACS will not benefit from endarterectomy or stenting unless it can be done with a risk <1%; TCD+ may benefit as much as SCS if their surgical risk is not higher. These findings suggest that ACS should be managed medically with delay of surgery or stenting until the occurrence of symptoms or emboli. (***Stroke***. **2005;36:2373-2378.**)

Key Words: asymptomatic carotid stenosis ■ endarterectomy ■ transcranial Doppler ■ ulcer ■ ultrasound ■ unstable plaque

LOYOLA MEDICINE

Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study

Hugh S Markus, Alice King, Martin Shipley, Raffi Topakian, Marisa Cullinane, Sheila Reihill, Natan M Bornstein, Arjen Schaafsma

Summary

Background Whether surgery is beneficial for patients with asymptomatic carotid stenosis is controversial. Better methods of identifying patients who are likely to develop stroke would improve the risk–benefit ratio for carotid endarterectomy. We aimed to investigate whether detection of asymptomatic embolic signals by use of transcranial doppler (TCD) could predict stroke risk in patients with asymptomatic carotid stenosis.

Methods The Asymptomatic Carotid Emboli Study (ACES) was a prospective observational study in patients with asymptomatic carotid stenosis of at least 70% from 26 centres worldwide. To detect the presence of embolic signals, patients had two 1 h TCD recordings from the ipsilateral middle cerebral artery at baseline and one 1 h recording at 6, 12, and 18 months. Patients were followed up for 2 years. The primary endpoint was ipsilateral stroke and transient ischaemic attack. All recordings were analysed centrally by investigators masked to patient identity.

Findings 482 patients were recruited, of whom 467 had evaluable recordings. Embolic signals were present in 77 of 467 patients at baseline. The hazard ratio for the risk of ipsilateral stroke and transient ischaemic attack from baseline to 2 years in patients with embolic signals compared with those without was 2·54 (95% CI 1·20–5·36; p=0·015). For ipsilateral stroke alone, the hazard ratio was 5·57 (1·61–19·32; p=0·007). The absolute annual risk of ipsilateral stroke or transient ischaemic attack between baseline and 2 years was 7·13% in patients with embolic signals and 3·04% in those without, and for ipsilateral stroke was 3·62% in patients with embolic signals and 0·70% in those without. The hazard ratio for the risk of ipsilateral stroke and transient ischaemic attack for patients who had embolic signals on the recording preceding the next 6-month follow-up compared with those who did not was 2·63 (95% CI 1·01–6·88; p=0·049), and for ipsilateral stroke alone the hazard ratio was 6·37 (1·59–25·57; p=0·009). Controlling for antiplatelet therapy, degree of stenosis, and other risk factors did not alter the results.

Interpretation Detection of asymptomatic embolisation on TCD can be used to identify patients with asymptomatic carotid stenosis who are at a higher risk of stroke and transient ischaemic attack, and also those with a low absolute stroke risk. Assessment of the presence of embolic signals on TCD might be useful in the selection of patients with asymptomatic carotid stenosis who are likely to benefit from endarterectomy.

Funding British Heart Foundation.

Lancet Neurol 2010; 9: 663–71
Published Online May 28, 2010
DOI:10.1016/S1474-4422(10)70120-4
See **Reflection and Reaction** page 644

Clinical Neuroscience, St George's University of London, London, UK (Prof H S Markus FRCP, A King MD, R Topakian MD, M Cullinane PhD, S Reihill BSc); **Department of Epidemiology and Public Health, University College London, London, UK** (M Shipley MSc); **Stroke Unit, Department of Neurology, Tel Aviv Sourasky Medical Center and Tel Aviv University, Tel Aviv, Israel** (Prof N M Bornstein MD); **and Department of Clinical Neurophysiology, Martini Ziekenhuis, Groningen, Netherlands** (A Schaafsma MD)

Correspondence to:
Prof Hugh Markus, Clinical Neuroscience, St George's University of London, Cranmer Terrace, London SW17 0RE, UK
h.markus@sghms.ac.uk

High-risk asymptomatic carotid stenosis

Ulceration on 3D ultrasound vs TCD microemboli

A. Madani, BSc
V. Beletsky, MD
A. Tamayo, MD
C. Munoz, MD, PhD
J.D. Spence, MD, FRCPC, FAHA

Address correspondence and reprint requests to Dr. J. David Spence, Stroke Prevention & Atherosclerosis Research Centre, 1400 Western Road, London, Ontario, Canada N6G 2V2
dspence@robarts.ca

ABSTRACT

Objective: We compared microemboli on transcranial Doppler (TCD) with carotid ulcerations on 3D ultrasound (US) as an additional method for identifying the small proportion of patients with asymptomatic carotid stenosis (ACS) who can benefit from revascularization such as endarterectomy or stenting.

Methods: Patients with ACS (n = 253) with carotid stenosis >60% by Doppler ultrasound were studied prospectively with TCD embolus detection and 3D US to detect ulcers (the total number of ulcers in both internal carotids) and followed for 3 years.

Results: Mean age was 69.66 (SD 8.51) years; 11 (4%) had ≥3 ulcers (Ulcer 3), 11 (6%) had microemboli, and 25 (10%) had microemboli or ≥3 ulcers. Ulcer 3 patients were more likely to have a stroke or death in 3 years (18% vs 2%; $p = 0.03$), regardless of the side on which the ulcers were found. The 3-year risk of stroke or death was 20% with microemboli vs 2% without ($p = 0.003$). The annual rate of ipsilateral stroke was 0.8%.

Conclusion: Adding 3D US detection of ulcers doubles (to 10%) the proportion of patients with ACS who may benefit from endarterectomy or stenting. However, until 3-year event rates of stroke or death with endarterectomy or stenting reach <2%, 90% of patients with ACS would be better treated medically until they develop symptoms, ulcers, or emboli. **Neurology® 2011;77:744–750**

LOYOLA MEDICINE

Available

One-Year Progression of Moderate Asymptomatic Carotid Stenosis Predicts the Risk of Vascular Events

Simona Balestrini, MD; Francesca Lupidi, MD; Clotilde Balucani, MD; Claudia Altamura, MD; Fabrizio Vernieri, MD; Leandro Provinciali, MD; Mauro Silvestrini, MD

Background and Purpose—This study aimed at evaluating whether ultrasound monitoring of moderate asymptomatic carotid stenosis may help in identifying subjects at high risk for vascular events.

Methods—We included 523 subjects with unilateral asymptomatic carotid stenosis of 50% to 69%. Follow-up carotid ultrasound was performed within 12 months from inclusion to detect the frequency and degree of stenosis progression. Subjects were prospectively evaluated for a median period of 42 months (interquartile range, 38–45) after a second ultrasound evaluation. Outcome measures were any stroke and transient ischemic attack, myocardial infarction, and death.

Results—Carotid stenosis progression was associated with the occurrence of vascular events (hazard ratio, 21.57; 95% confidence interval, 11.81–39.39; $P<0.001$). During follow-up, 96.7% of subjects without progressive carotid stenosis remained free from vascular events. Among patients with progressive stenosis, 53.7% experienced a vascular event and 27.1% experienced an ipsilateral stroke.

Conclusions—One-year moderate asymptomatic carotid stenosis progression is related to higher risk of vascular events, including ipsilateral stroke. (***Stroke*. 2013;44:792-794.**)

LOYOLA MEDICINE

Carotid Plaque MRI and Stroke Risk

A Systematic Review and Meta-analysis

Ajay Gupta, MD; Hediyeh Baradaran, MD; Andrew D. Schweitzer, MD; Hooman Kamel, MD; Ankur Pandya, PhD; Diana Delgado, MLS; Allison Dunning, MS; Alvin I. Mushlin, MD, ScM; Pina C. Sanelli, MD, MPH

Background and Purpose—MRI characterization of carotid plaque has been studied recently as a potential tool to predict stroke caused by carotid atherosclerosis. We performed a systematic review and meta-analysis to summarize the association of MRI-determined intraplaque hemorrhage, lipid-rich necrotic core, and thinning/rupture of the fibrous cap with subsequent ischemic events.

Methods—We performed a comprehensive literature search evaluating the association of carotid plaque composition on MRI with ischemic outcomes. We included cohort studies examining intraplaque hemorrhage, lipid-rich necrotic core, or thinning/rupture of the fibrous cap with mean follow-up of ≥1 month and an outcome measure of ipsilateral stroke or transient ischemic attack. A meta-analysis using a random-effects model with assessment of study heterogeneity and publication bias was performed.

Results—Of the 3436 articles screened, 9 studies with a total of 779 subjects met eligibility for systematic review. The hazard ratios for intraplaque hemorrhage, lipid-rich necrotic core, and thinning/rupture of the fibrous cap as predictors of subsequent stroke/transient ischemic attack were 4.59 (95% confidence interval, 2.91–7.24), 3.00 (95% confidence interval, 1.51–5.95), and 5.93 (95% confidence interval, 2.65–13.20), respectively. No statistically significant heterogeneity or publication bias was present in the 3 main meta-analyses performed.

Conclusions—The presence of intraplaque hemorrhage, lipid-rich necrotic core, and thinning/rupture of the fibrous cap on MRI of carotid plaque is associated with increased risk of future stroke or transient ischemic attack in patients with carotid atherosclerotic disease. Dedicated MRI of plaque composition offers stroke risk information beyond measurement of luminal stenosis in carotid atherosclerotic disease. (***Stroke*. 2013;44:3071-3077.**)

Progression Rate and Ipsilateral Neurological Events in Asymptomatic Carotid Stenosis

Liam S. Hirt, MBBS, MRCP

Background and Purpose—Progression of asymptomatic carotid stenoses with >50% luminal narrowing is associated with an increased risk of stroke. The significance of the progression rate in these patients is unknown. The main aim of this study was to evaluate the rate of change of carotid luminal narrowing over 1 year, as a risk factor for ipsilateral ischemic events, in patients with a >50% asymptomatic carotid stenosis. Secondary aims were to establish the incidence of changes in carotid luminal narrowing and establish additional risk factors for ipsilateral neurological events.

Methods—A retrospective analysis was conducted of data derived from the deferred endarterectomy arm of the Asymptomatic Carotid Surgery Trial. Patients were followed up for ≥5 years with serial carotid duplex examinations. Data were derived from information obtained at randomization and annual follow-up visits with carotid duplex examination. Potential risk factors for ipsilateral neurological events were analyzed in Poisson regression models.

Results—Data from 1469 patients were included. Two hundred forty-four had ipsilateral events; 240 had ipsilateral carotid surgery; 370 died from nonstroke causes; and 82 had an asymptomatic carotid occlusion. The annual incidence of progression in the cohort as a whole was 5.2%. Ipsilateral events occurred in 17% of patients. Diabetes and previous contralateral symptoms showed a significant independent association with ipsilateral neurological events. Ipsilateral events were associated with high rates of progression over 1 year but not with low progression rates or regression.

Conclusions—Fast rates of progression of carotid luminal narrowing should be interpreted as a sign of significantly increased risk of future ipsilateral neurological events. (***Stroke*. 2014;45:702-706.**)

Clin Neuroradiol
DOI 10.1007/s00062-015-0403-1

REVIEW ARTICLE

The Past, Present and Future of Endovascular Aneurysm Treatment

H. Henkes · W. Weber

Received: 1 April 2015 / Accepted: 28 April 2015

Abstract The technology available for the endovascular treatment of intracranial aneurysms is rapidly evolving. Both current and future devices are described. This includes, among others, UNO for parent vessel occlusion, the Medina device for saccular filling, the Comaneci device for remodeling, pCONus for assisted coil occlusion, and WEB and pCANvas for intrasaccular flow disruption. Perspectives of further development such as surface coating for increased radioopacity and decreased thrombogenicity are explained.

Keywords Aneurysm · Endovascular · Coil · Stent · Flow diversion

The Past

The idea to treat intracranial aneurysms from within the arterial system and avoiding surgical exposure was proposed in the 1960s [1]. Initial success was achieved by parent vessel occlusion using detachable balloons [2]. The intrasaccular balloon deployment, however, was associated with significant risks [3]. The dawn of endovascular aneurysm treatment started 25 years ago, when the first manufactured endovascular devices became available. Until then, physicians assembled microcatheters and balloons on site under adventurous circumstances.

A major advance came with the development of electrolytically detachable coils [4]. For the first time, a controlled and atraumatic intrasaccular treatment became feasible. During the evolution of neuroendovascular treatment concepts and products it was common that the initially intended mode of operation (e.g., electrothrombosis) turned out to be inefficient [5]. The possibility to remove the coil from the aneurysm or to detach it added safety and efficacy to this treatment modality.

Subsequently, coil variants with different detachment mechanisms (e.g., electrothermal, hydraulic, etc.), featuring varying stiffness and different shapes became available. It soon became apparent that aneurysms with a neck of ≥4 mm were frequently less suitable for straightforward coil occlusion. Balloon remodeling [6] advanced the technique by providing balloon-assisted coiling, thus improving occlusion rates and packing density. An alternative was the deployment of a balloon expandable coronary stent [7]. Balloon-mounted stents were, however, stiff and the balloon inflation for stent deployment in front of an aneurysm was not without risk. This led to the development of a highly flexible, self-expanding open-cell design stent (Neuroform, Smart Therapeutics) [8]. Closed-cell, braided (Leo, Balt) and laser cut stents (Enterprise, Cordis [9]) and a detachable stent (Solitaire, ev3 [10]) followed thereafter. Other developments such as the first bioactive coil (Matrix, Boston Scientific [11]) and Onyx HD500 for aneurysms (ev3, Irvine [12]) were, at least in retrospect, failures.

H. Henkes (✉)
Klinik für Neuroradiologie, Neurozentrum,
Klinikum Stuttgart,
Stuttgart, Germany
e-mail: hhhenkes@aol.com

W. Weber
Institut für Diagnostische und Interventionelle Radiologie,
Neuroradiologie und Nuklearmedizin, Universitätsklinikum
Knappschaftskrankenhaus Bochum,
Bochum, Germany

Published online: 02 June 2015

Journal of Thrombosis and Haemostasis, **4**: 295–306

SPECIAL ARTICLE

International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS)

S. MIYAKIS,* M. D. LOCKSHIN,† T. ATSUMI,‡ D. W. BRANCH,§ R. L. BREY,¶ R. CERVERA,** R. H. W. M. DERKSEN,†† P. G. DE GROOT,†† T. KOIKE,‡ P. L. MERONI,‡‡ G. REBER,§§ Y. SHOENFELD,¶¶ A. TINCANI,*** P. G. VLACHOYIANNOPOULOS††† and S. A. KRILIS*

*St George Hospital, University of New South Wales, Sydney, Australia; †Hospital for Special Surgery, Cornell Medical Center, New York, NY, USA; ‡Hokkaido University, Sapporo, Japan; §University of Utah Health Sciences Center, Salt Lake City, UT; ¶University of Texas Health Science Center, San Antonio, TX, USA; **Hospital Clinic, Barcelona, Spain; ††University Medical Center, Utrecht, The Netherlands; ‡‡Istituto Auxologico Italiano, University of Milan, Milan, Italy; §§University Hospital, Geneva, Switzerland; ¶¶Sheba Medical Center, Tel-Hashomer and Tel Aviv University, Israel; ***Spedali Civili, University of Brescia, Italy; and †††Department of Pathophysiology, University of Athens, Greece*

To cite this article: Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RHWM, de Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; **4**: 295–306.

Summary. New clinical, laboratory and experimental insights, since the 1999 publication of the Sapporo preliminary classification criteria for antiphospholipid syndrome (APS), had been addressed at a workshop in Sydney, Australia, before the Eleventh International Congress on antiphospholipid antibodies. In this document, we appraise the existing evidence on clinical and laboratory features of APS addressed during the forum. Based on this, we propose amendments to the Sapporo criteria. We also provide definitions on features of APS that were not included in the updated criteria.

for APS. Members of the workshop panel included all of the authors and the individuals listed in the Appendix.

Some of the authors presented the current evidence in their area of expertise (see Addendum) providing relevant literature on predictors of outcome, risk factors, associations between clinical and laboratory features and accuracy of tests. The evidence was also reviewed and graded (according to criteria listed in Table 1) by three members of the committee (SM, MDL, SAK) not involved in the presentation of specific topics. An open discussion followed, to reach consensus. Where data were limited or incongruent, expert opinion supplements the

Journal of Thrombosis and Haemostasis, **3**: 292–299

ORIGINAL ARTICLE

Homocysteine, *MTHFR* and risk of venous thrombosis: a meta-analysis of published epidemiological studies

M. DEN HEIJER,* S. LEWINGTON† and R. CLARKE†

**Department of Endocrinology and Epidemiology and Biostatistics, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; and †Clinical Trial Service Unit and Epidemiological Studies Unit, Radcliffe Infirmary, University of Oxford, Oxford, UK*

To cite this article: den Heijer M, Lewington S, Clarke R. Homocysteine, *MTHFR* and risk of venous thrombosis: a meta-analysis of published epidemiological studies. *J Thromb Haemost* 2005; **3**: 292–9.

Summary. *Context*: It has been suggested that elevated total plasma homocysteine levels are associated with the risk of venous thrombosis. *Objective*: To assess the relationship of homocysteine and the *MTHFR* 677TT genotype and the risk of venous thrombosis by conducting a meta-analysis of all relevant studies. *Data sources and selection*: Studies (case–control or nested case–control) were identified by searches of electronic literature for relevant reports published before July 2003 on homocysteine and the *MTHFR* 677TT genotype and venous thrombosis as an end-point, by hand-searching reference lists of original articles (including meta-analyses) on this topic and by contact with investigators in the field. *Data extraction*: A meta-analysis of 24 retrospective (n = 3289 cases) and three prospective studies (n = 476 cases) was carried out to examine the association of homocysteine with venous thrombosis. A meta-analysis of 53 studies (n = 8364 cases) of the *MTHFR* 677TT genotype (that increases homocysteine) was carried out to assess if this association is causal. *Data synthesis*: A 5 μmol L^{-1} higher measured homocysteine level was associated with a 27% (95% CI: 1–59) higher risk of venous thrombosis in prospective studies and a 60% (95% CI: 10–134) higher risk in retrospective studies. The 677TT genotype was associated with a 20% (95% CI: 8–32) higher risk of venous thrombosis compared with the 677CC genotype. In contrast with non-American studies, the 677TT genotype had no effect on venous thrombosis in North America, due probably to the higher intake of folate and riboflavin in North America. *Conclusion*: This meta-analysis of prospective and retrospective studies demonstrates a modest association of homocysteine with venous thrombosis. The elevated risk associated with the MTHFR 677TT genotype provides some support for causality.

Keywords: homocysteine, MTHFR, venous thrombosis.

Introduction

Venous thrombosis, including deep-vein thrombosis and pulmonary embolism, is an important cause of morbidity and mortality, particularly in older people [1]. Most cases of venous thrombosis arise due to prolonged immobilization, major surgery, trauma or cancer, but genetic or acquired hemostatic abnormalities, including elevated plasma homocysteine levels, have also been implicated [2]. The initial epidemiological evidence that examined the association between homocysteine and venous thrombosis was derived from retrospective case–control studies (in which blood for homocysteine measurements was collected after onset of thrombotic events in cases) [3–7], but it was not possible to ascertain whether the higher homocysteine levels caused the thrombotic event or was a consequence of it. Subsequently, prospective studies (in which blood for homocysteine measurements was collected before the onset of the thrombotic events) appeared to confirm these findings, but the weaker results raised questions about causality [8–10].

Elucidation of an association between a genetic variant associated with elevated homocysteine levels and venous thrombosis might be informative about the hypothesis that higher levels of homocysteine plays a causal role in the occurrence of venous thrombosis [11]. Studies of genetic variants that affect homocysteine levels would reflect long-term differences in homocysteine, and be independent of confounding and concerns about reverse causality [11]. A common polymorphism exists in the gene that encodes the catalytic domain of the *MTHFR* enzyme, in which a

Journal of Thrombosis and Haemostasis, **3**: 79–84

ORIGINAL ARTICLE

Elevated levels of FVIII:C within families are associated with an increased risk for venous and arterial thrombosis

I. BANK,* E. J. LIBOUREL,† S. MIDDELDORP,* K. HAMULYÁK,‡ E. C. M. VAN PAMPUS,† M. M. W. KOOPMAN,* M. H. PRINS,§ J. VAN DER MEER† and H. R. BÜLLER*

**Department of Vascular Medicine, Academic Medical Center, University of Amsterdam; †Department of Hematology, Division of Hemostasis, Thrombosis, and Rheology, University Hospital Groningen; ‡Department of Hematology, University Hospital of Maastricht, Maastricht; and §Department of Clinical Epidemiology and Medical Technology Assessment, University Hospital of Maastricht, Maastricht, the Netherlands*

To cite this article: Bank I, Libourel EJ, Middeldorp S, Hamulyák K, van Pampus ECM, Koopman MMW, Prins MH, van der Meer J, Büller HR. Elevated levels of FVIII:C within families are associated with an increased risk for venous and arterial thrombosis. *J Thromb Haemost* 2005; **3**: 79–84.

Summary. Elevated levels of coagulation factor VIII:C (FVIII:C) are associated with an increased risk for venous and arterial thromboembolism. Whether relatives of patients with elevated levels of FVIII:C are also at increased risk for thrombotic disease is unknown. The objective was to determine the annual incidences of both venous and arterial thrombotic events in first-degree relatives of patients with elevated levels of FVIII:C and venous thromboembolism (VTE) or premature atherosclerosis. A retrospective study with 584 first-degree relatives of 177 patients with elevated levels of FVIII:C was performed. The level of FVIII:C was determined and relatives with elevated and normal levels of FVIII:C were compared. Of the participants, 40% had elevated levels of FVIII:C. The annual incidence of a first episode of VTE was 0.34% and 0.13% in relatives with elevated levels of FVIII:C and those with normal levels, respectively [OR 3.7 (95% CI 1.9–7.5)]. The absolute annual incidence in the youngest age group with elevated levels of FVIII:C was 0.16% (0.05–0.37) and gradually increased to 0.99% (0.40–2.04) in those older than 60 years of age, although the odds ratios were not statistically significant. The annual incidences of a first arterial thrombotic event were 0.29% and 0.14% in relatives with and without elevated levels of FVIII:C, respectively [OR 3.1 (1.4–6.6)]. In particular the risks for a first myocardial infarction [OR 4.3 (1.0–18.1); P = 0.046] and a first peripheral arterial thrombosis [OR 8.6 (1.6–47.6)] were increased. Within families of patients with elevated levels of FVIII:C and VTE or premature atherosclerosis, 40% of their first-degree relatives has elevated levels of FVIII:C as well, and they are at increased risk for both VTE and arterial thrombosis as compared with their relatives with normal levels.

Keywords: arterial thrombosis, family study, FVIII:C, premature atherosclerosis, venous thromboembolism.

Introduction

Elevated levels of coagulation factor VIII (FVIII:C) increase the risk for venous thromboembolism (VTE), with each 10 IU dL^{-1} increment resulting in a 10% risk increase for VTE [1,2]. Furthermore, patients known with elevated levels of FVIII:C may also be at risk for recurrent VTE [3,4]. Besides VTE, elevated levels of FVIII:C have been associated with arterial thrombotic diseases, in particular acute myocardial infarction, ischemic stroke and peripheral arterial thrombotic disease [5–7].

As elevated levels of FVIII:C are, at least partially, determined genetically [3,8–10], the question arises whether relatives of patients with elevated levels of FVIII:C also have higher levels of this clotting factor, and whether they are at increased risk for VTE and arterial thrombotic disease.

Therefore, we determined the prevalence of elevated levels of FVIII:C and calculated the absolute risks for VTE and arterial thrombotic disease in first-degree relatives of consecutive patients with VTE or premature atherosclerosis and elevated levels of FVIII:C.

Thrombophilia: 2009 Update

Pat Foy, MD
Stephan Moll, MD

Corresponding author
Stephan Moll, MD
Department of Medicine, Division of Hematology-Oncology, University of North Carolina School of Medicine, CB7035, Chapel Hill, NC 27599, USA.
E-mail: smoll@med.unc.edu

Current Treatment Options in Cardiovascular Medicine 2009, **11**:114–128
Current Medicine Group LLC ISSN 1092-8464

Opinion statement

As venous thrombosis is mostly caused by disturbances in the plasma coagulation system, abnormalities of coagulation factors are mostly risk factors for venous thromboembolism (VTE). Relatively little is known about thrombophilias that predispose to arterial thromboembolism. Although some abnormalities in the fibrinolytic pathway appear to predispose to arterial thrombosis, the associations are weak and often inconsistent between studies. At present, there is not enough consistent and clinically meaningful information to include fibrinolytic parameters in a clinical thrombophilia workup. Controversy exists as to which patients and family members to test for thrombophilia. Several testing guidelines exist. Routine screening for inherited thrombophilias is not indicated in patients with VTE provoked by immobility, surgery, and malignancy, or in those with arterial thrombosis with arteriosclerosis risk factors. Heterozygous factor V Leiden (FVL) and prothrombin 20210 mutations increase the risk for recurrent VTE only slightly once anticoagulation is stopped. Therefore, decisions regarding the length of anticoagulant therapy typically are not influenced by finding one of these heterozygous mutations. The main reason to perform thrombophilia testing in a patient is to detect a strong thrombophilia (ie, antithrombin deficiency, antiphospholipid antibody syndrome, homozygous FVL, double-heterozygous FVL plus prothrombin 20210 mutation, protein C deficiency, and maybe protein S deficiency). The finding of a strong thrombophilia has several clinical consequences: it decreases the threshold to recommend long-term anticoagulation in a patient with unprovoked VTE; facilitates discussion regarding whether anticoagulant or antiplatelet therapy is the preferred empiric treatment for a patient who had an unexplained arterial, nonarteriosclerotic thromboembolic event; and leads to the consideration of testing asymptomatic female family members for the identified thrombophilia(s) so they can be counseled on their risk of thromboembolism, the use of hormonal therapies, and the potential benefit of pre- and postpartum anticoagulant therapy.

Review article

Anti–β2-glycoprotein I, antiprothrombin antibodies, and the risk of thrombosis in the antiphospholipid syndrome

Monica Galli, Davide Luciani, Guido Bertolini, and Tiziano Barbui

The association of antiphospholipid antibodies with thrombosis and obstetric events defines the antiphospholipid syndrome. A recent systematic review of the literature showed lupus anticoagulants to be risk factors of thrombosis, independent of the type and site of the event, the presence of systemic lupus erythematosus, and the laboratory methods used to detect them. Anticardiolipin antibodies were not such strong risk factors, unless arterial thrombosis, the G isotype, and medium or high titers were considered. Here, we extended the systematic review to anti–β2-glycoprotein I and antiprothrombin antibodies. Thirty-two mainly retrospective studies provided or enabled us to calculate the odds ratio (OR) with a 95% confidence interval (CI) of anti–β2-glycoprotein I and antiprothrombin antibodies for thrombosis in 5102 patients and 1973 controls. Twenty-eight studies analyzed 60 associations between anti–β2-glycoprotein I antibodies and thrombosis: 5 of 17 associations with arterial thrombosis, 12 of 21 with venous events, and 17 of 22 with any type of thrombosis were significant. Seventeen studies assessed 46 associations between antiprothrombin antibodies and thrombosis: only 17 were significant. As most studies involved patients with systemic lupus erythematosus, lupus anticoagulants, or anticardiolipin antibodies, it is difficult to establish the value of anti–β2-glycoprotein I and antiprothrombin antibodies as independent risk factors. In conclusion, the clinical significance of these antibodies still requires further investigation. However, before other clinical studies are done, standardization or at least harmonization of the methods used to detect anti–β2-glycoprotein I and antiprothrombin antibodies is mandatory.

abortions before the tenth week. All other causes of pregnancy morbidity must be excluded.

Antiphospholipid antibodies are a wide and heterogeneous family of immunoglobulin G (IgG) and/or IgM, or less frequently also IgA, immunoglobulins, long considered to react with negatively charged phospholipids. Lupus anticoagulants and anticardiolipin antibodies were the first 2 such antibodies to be described. Lupus anticoagulants behave as acquired inhibitors of coagulation, prolonging phospholipid-dependent coagulation,[4] and anticardiolipin antibodies are usually identified by immunoassays with cardiolipin or other anionic phospholipids in solid phase.[5]

The "Sapporo" laboratory criteria for definite antiphospholipid syndrome are as follows: lupus anticoagulants and/or anticardiolipin antibodies must be present on 2 or more occasions at least 6 weeks apart[1]; lupus anticoagulants must be diagnosed according to the criteria proposed by the Scientific Subcommittee of Standardization of Lupus Anticoagulants/Phospholipid-dependent Antibodies[6]; anticardiolipin antibodies must be measured by a "standardized" enzyme-linked immunosorbent assay (ELISA) for β2-glycoprotein I–dependent antibodies; and IgG and/or IgM anticardiolipin antibodies have to be present at medium or high titers. According to the Sapporo definition, definite antiphospholipid syndrome is established when at least one clinical and one laboratory criteria are met.

To support the inclusion of lupus anticoagulants and anticardiolipin antibodies as laboratory criteria for the antiphospholipid syndrome in relation to thrombosis, we performed a systematic computer-assisted (MEDLINE) search of the literature published in the English language from 1988 through 2001. There were 25

Primary thromboprophylaxis in patients with antiphospholipid antibodies

LOYOLA MEDICINE

	Primary thromboprophylaxis
Patients with systemic lupus erythematosus and lupus anticoagulant and/or persistently positive anticardiolipin	Hydroxychloroquine and consider low-dose aspirin
Patients with obstetric antiphospholipid syndrome	Low-dose aspirin or no therapy
Asymptomatic carriers of antiphospholipid antibodies	No therapy or low-dose aspirin
All patients with antiphospholipid antibodies	Strict control of vascular risk factors
High-risk situations (surgery, post partum, long-lasting immobilisation)	Adequate thrombophylaxis

Lancet 2010;376:1498-1509

Recommendations for secondary prophylaxis in patients with antiphospholipid antibodies

LOYOLA MEDICINE

	Secondary prophylaxis
Patients with definite antiphospholipid syndrome and first venous event*	Indefinite anticoagulation to a target INR 2·0–3·0
Patients with definite antiphospholipid syndrome and arterial event*	Indefinite anticoagulation to a target INR 3·0–4·0 or combined antithrombotic treatment
Patients with definite antiphospholipid syndrome and recurrent events despite warfarin with a target intensity of 2·0–3·0	Indefinite anticoagulation to a target INR 3·0–4·0 or alternative therapies such as extended therapeutic dose low-molecular-weight heparin
Patients with venous thromboembolism with single positive or low-titre antiphospholipid antibodies	As per usual recommendations for deep vein thrombosis treatment
Patients with arterial thrombosis with single positive or low-titre antiphospholipid antibodies	As per usual recommendations for arterial thrombosis

INR=international normalised ratio. *Less aggressive or long-lasting antithrombotic treatments might be appropriate in low-risk patients.

Lancet 2010;376:1498-1509

Suggested regimens for the treatment of antiphospholipid syndrome in pregnancy

LOYOLA MEDICINE

	Regimen
Antiphospholipid syndrome without previous thrombosis and recurrent early (pre-embryonic or embryonic) miscarriage	Low-dose aspirin alone or together with either unfractionated heparin (5000–7500 IU subcutaneously every 12 h) or LMWH (usual prophylactic doses)
Antiphospholipid syndrome without previous thrombosis and fetal death (more than 10 weeks' gestation) or previous early delivery (<34 weeks gestation) due to severe pre-eclampsia or placental insufficiency	Low-dose aspirin plus: • Unfractionated heparin (7500–10 000 IU subcutaneoulsy every 12 h in the first trimester; 10 000 U subcutaneously every 12 h in the second and third trimesters, or every 8–12 h adjusted to maintain the mid-interval aPTT* 1·5 times the control mean) • LMWH (usual prophylactic doses)
Antiphospholipid syndrome with thrombosis	Low-dose aspirin plus: • Unfractionated heparin (subcutaneously every 8–12 h adjusted to maintain the mid-interval aPTT* or heparin concentration (anti-Xa activity)* in the therapeutic range) • LMWH (usual therapeutic dose—eg, enoxaparin 1 mg/kg subcutaneously, or dalteparin 100 U/kg subcutaneously every 12 h, or enoxaparin 1·5 mg/kg/day subcutanously, or dalteparin 200 U/kg/day subcutaneously)†

Lancet 2010;376:1498-1509

LOYOLA MEDICINE

VIEWS & REVIEWS

International consensus diagnostic criteria for neuromyelitis optica spectrum disorders

OPEN

Dean M. Wingerchuk, MD, FRCP(C)
Brenda Banwell, MD, FRCP(C)
Jeffrey L. Bennett, MD, PhD
Philippe Cabre, MD
William Carroll, MD
Tanuja Chitnis, MD
Jérôme de Seze, MD
Kazuo Fujihara, MD
Benjamin Greenberg, MD
Anu Jacob, MD
Sven Jarius, MD
Marco Lana-Peixoto, MD

ABSTRACT

Neuromyelitis optica (NMO) is an inflammatory CNS syndrome distinct from multiple sclerosis (MS) that is associated with serum aquaporin-4 immunoglobulin G antibodies (AQP4-IgG). Prior NMO diagnostic criteria required optic nerve and spinal cord involvement but more restricted or more extensive CNS involvement may occur. The International Panel for NMO Diagnosis (IPND) was convened to develop revised diagnostic criteria using systematic literature reviews and electronic surveys to facilitate consensus. The new nomenclature defines the unifying term NMO spectrum disorders (NMOSD), which is stratified further by serologic testing (NMOSD with or without AQP4-IgG). The core clinical characteristics required for patients with NMOSD with AQP4-IgG include clinical syndromes or MRI findings related to optic nerve, spinal cord, area postrema, other brainstem, diencephalic, or cerebral presentations. More stringent clinical criteria, with additional neuroimaging findings, are required for diagnosis of NMOSD without AQP4-IgG or when serologic testing is unavailable. The IPND also proposed validation strategies and achieved consensus on pediatric NMOSD diagnosis and the concepts of monophasic NMOSD and opticospinal MS. *Neurology*® 2015;85:177–189

Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *The Year in Neurology and Psychiatry*

Neuromyelitis optica and the evolving spectrum of autoimmune aquaporin-4 channelopathies: a decade later

Sean J. Pittock[1,2] and Claudia F. Lucchinetti[2]

[1]Department of Laboratory Medicine/Pathology, Rochester, Minnesota. [2]Department of Neurology, Mayo Clinic, College of Medicine, Rochester, Minnesota

Address for correspondence: Sean J. Pittock, Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. pittock.sean@mayo.edu

The discovery of AQP4-IgG (a pathogenic antibody that targets the astrocytic water channel aquaporin-4), as the first sensitive and specific biomarker for any inflammatory central nervous system demyelinating disease (IDD), has shifted emphasis from the oligodendrocyte and myelin to the astrocyte as a central immunopathogenic player. Neuromyelitis optica (NMO) spectrum disorders (SDs) represent an evolving spectrum of IDDs extending beyond the optic nerves and spinal cord to include the brain (especially in children) and, rarely, muscle. NMOSD typical brain lesions are located in areas that highly express the target antigen, AQP4, including the circumventricular organs (accounting for intractable nausea and vomiting) and the diencephalon (accounting for sleep disorders, endocrinopathies, and syndrome of inappropriate antidiuresis). Magnetic resonance imaging brain abnormalities fulfill Barkoff criteria for multiple sclerosis in up to 10% of patients. As the spectrum broadens, the importance of highly specific assays that detect pathogenic AQP4-IgG targeting extracellular epitopes of AQP4 cannot be overemphasized. The rapid evolution of our understanding of the immunobiology of AQP4 autoimmunity necessitates continuing revision of NMOSD diagnostic criteria. Here, we describe scientific advances that have occurred since the discovery of NMO-IgG in 2004 and review novel targeted immunotherapies. We also suggest that NMOSDs should now be considered under the umbrella term *autoimmune aquaporin-4 channelopathy*.

Established in 1871
SMW
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Review article: Current opinion | Published 23 September 2014, doi:10.4414/smw.2014.14012
Cite this as: Swiss Med Wkly. 2014;144:w14012

Update on multiple sclerosis treatments

Claire Bridel[a], Patrice H. Lalive[a,b]

[a] Department of Clinical Neurosciences, Division of Neurology, Unit of Neuroimmunology and Multiple Sclerosis, Geneva University Hospital and Faculty of Medicine of the University of Geneva, Switzerland
[b] Department of Genetic and Laboratory Medicine, Division of Laboratory Medicine, Geneva University Hospital, Switzerland

Summary

Relapsing-remitting multiple sclerosis (RRMS) management has dramatically changed over the past decade. New drugs have arrived on the market, allowing for more individualised treatment selection. However, this diversity has increased the complexity of RRMS patient follow-up. In this review, we provide summarised information about treatment efficacy, potential side-effects, follow-up recommendations, vaccinations, and pregnancy safety issues for all currently available disease modifying therapies and those awaiting approval.

Key words: *Multiple sclerosis; disease modifying therapies; recommendations; fingolimod; interferon beta; glatiramer acetate; teriflunomide; dimethyl fumarate*

initiation [3, 4]. Approved as a first-line treatment in Switzerland in 2011, fingolimod is the first oral treatment of RRMS. In the European Union, fingolimod is approved as a second-line treatment, except for patients with highly active RRMS for whom it can be prescribed as a first-line therapy.

Fingolimod 0.5 mg once daily reduced annualised relapse rate (ARR) by 54% compared to placebo in phase III trial FREEDOMS [3]. Both risk of disability progression and MRI evidence of disease activity (number of gadolinium-enhancing lesions and volume of hypointense lesions on T1–weighted scans, median volume of lesions and number of new/enlarged lesions on T2–weighted scans) were significantly reduced in fingolimod-treated patients [3]. In phase III trial TRANSFORMS [4], fingolimod was more effective in reducing ARR compared to weekly intramuscular interferon beta-1a (Avonex®), but there was no benefit of

CrossMark

Update on treatments in multiple sclerosis

Laure Michel, Catherine Larochelle, Alexandre Prat

Available online: 23 March 2015

Université de Montréal, faculté de médecine, centre de recherche du CHUM, département de neuroscience, unité de recherche en neuro-immunologie, H2X0A9 Montréal, Canada

Correspondence:
Alexandre Prat, CRCHUM, 900, rue Saint-Denis, 9e étage, H2X0A9 Montréal, Québec, Canada.
a.prat@umontreal.ca

In this issue

Multiple sclerosis: from new concepts to updates on management
David-Axel Laplaud, Nantes, France

The autoimmune concept of multiple sclerosis
Bryan Nicol et al., Nantes, France

Environmental factors in multiple sclerosis
Vasiliki Pantazou et al., Lausanne, Switzerland

Update on clinically isolated syndrome

Summary

While there is no cure for multiple sclerosis (MS), numerous disease-modifying drugs are now available to treat MS patients. In fact, the therapeutic strategies are now more and more complex, directly impacting the management of patients. Despite the good safety profile of the first-line immunomodulatory drugs, the clinical response is often suboptimal. Important questions remain about the right timing to switch for a second-line agent and whether escalation therapy is an appropriate therapeutic strategy. In this review, we conducted a systematic search by PubMed using the terms: treatment, multiple sclerosis, therapeutic, DMT and treatment response. Randomized trials and reviews addressing MS, DMTs and management strategies were selected and included in this review. Herein, we present the currently approved and emerging drugs used for the treatment of MS with their relative benefit/risk profiles, and their respective positions in the therapeutic arsenal. We then focused on the different therapeutic strategies and criteria available to evaluate the response to disease-modifying therapies (DMTs).

Review Article

Update on Disease-Modifying Treatments for Multiple Sclerosis

Michael D. Carrithers, MD, PhD

Neurology Service, William S. Middleton Memorial Veterans Hospital, Departments of Neurology and Pathology and Program in Cellular and Molecular Pathology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

ABSTRACT

Purpose: The purpose of this review is to discuss the selection and use of disease- modifying treatments for patients with relapsing forms of multiple sclerosis (MS).

Methods: PubMed was searched (1966–2014) using the terms *multiple sclerosis, treatment, interferon, glatiramer acetate, dimethyl fumarate, fingolimod, teriflunomide, natalizumab, rituximab*, and *alemtuzumab*.

Findings: MS is a chronic neurological disorder that can cause a substantial degree of disability. Because of its usual onset in young adults, patients may require treatment for several decades. Currently available agents include platform injectable therapies, newer oral agents, and second-line monoclonal antibody treatments. Treatment decisions have become more complex with the introduction of new approaches, and a major goal is to balance perceived efficacy and tolerability in a specific patient with the relative impact of disease activity and adverse events on quality of life. Here the options for disease-modifying treatments for relapsing forms of MS are reviewed, and current and future challenges are discussed.

Implications: An evidence-based approach can be used for the selection of disease-modifying treatments based on disease phenotype and severity, adverse events, and perceived efficacy. (*Clin Ther.* 2014;36:1938–1945) Published by Elsevier HS Journals, Inc.

Key Words: immune therapy, multiple sclerosis, interferon, glatiramer, natalizumab, fumarate.

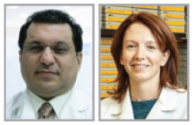
INTRODUCTION

Multiple sclerosis (MS) is the most common cause of nontraumatic neurological disability in young adults and has a high personal and societal impact on quality of life and health-care costs.[1] Many options currently exist to treat relapsing forms of MS. These include platform injectable therapies, newer oral options, and targeted monoclonal antibody agents for those who require more aggressive therapy. All of these approaches have demonstrated efficacy at reducing the number of clinical relapses and appearance of new lesions on imaging. Although effects on long-term outcome are less clear, there is evidence that early treatment can reduce long-term mortality associated with MS disability.[2,3]

All current disease-modifying treatments modulate or suppress immune function, particularly within lymphocyte subsets.[4] The success of these approaches combined with numerous studies on immunology,[5,6] pathogenesis,[7,8] and genetics[9] has confirmed that MS is an immune-mediated disorder of the central nervous system (CNS). Because of the relatively high incidence of MS in some populations and the ability to monitor disease activity clinically and radiologically, the development of MS therapeutics has been at the leading edge of translational research in autoimmune and neuro-

EDITORIAL
For reprint orders, please contact: reprints@futuremedicine.com

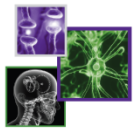
Stem cell therapy in multiple sclerosis: a future perspective



"A more recent concern in the field of mesenchymal stem cells-based therapies relates to the impact of cryopreservation on the therapeutic properties of the cells."

Violaine K Harris[1] & Saud A Sadiq*[1]

Neurodegenerative Disease Management



F1000Prime REPORTS

Published: 26 May 2015

Recent treatment advances and novel therapeutic approaches in epilepsy

Enrique Serrano and Andres M. Kanner*

Address: Department of Neurology, University of Miami, Miller School of Medicine, 1120 NW 14th Street, Miami, FL 33136, USA

* Corresponding author: Andres M. Kanner (a.kanner@med.miami.edu)

F1000Prime Reports 2015, **7**:61 (doi:10.12703/P7-61)

Abstract

The purpose of this article is to review recent advances in the treatment of epilepsy. It includes five antiepileptic drugs that have been recently added to the pharmacologic armamentarium and surgical techniques that have been developed in the last few years. Finally, we review ongoing research that may have a potential role in future treatments of epilepsy.

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY.

Evidence-based guideline: Management of an unprovoked first seizure in adults

Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society

Allan Krumholz, MD
Samuel Wiebe, MD
Gary S. Gronseth, MD
David S. Gloss, MD
Ana M. Sanchez, MD
Arif A. Kabir, MD
Aisha T. Liferidge, MD
Justin P. Martello, MD
Andres M. Kanner, MD
Shlomo Shinnar, MD, PhD
Jennifer L. Hopp, MD
Jacqueline A. French, MD

Correspondence to American Academy of Neurology: guidelines@aan.com

ABSTRACT

Objective: To provide evidence-based recommendations for treatment of adults with an unprovoked first seizure.

Methods: We defined relevant questions and systematically reviewed published studies according to the American Academy of Neurology's classification of evidence criteria; we based recommendations on evidence level.

Results and recommendations: Adults with an unprovoked first seizure should be informed that their seizure recurrence risk is greatest early within the first 2 years (21%–45%) (Level A), and clinical variables associated with increased risk may include a prior brain insult (Level A), an EEG with epileptiform abnormalities (Level A), a significant brain-imaging abnormality (Level B), and a nocturnal seizure (Level B). Immediate antiepileptic drug (AED) therapy, as compared with delay of treatment pending a second seizure, is likely to reduce recurrence risk within the first 2 years (Level B) but may not improve quality of life (Level C). Over a longer term (>3 years), immediate AED treatment is unlikely to improve prognosis as measured by sustained seizure remission (Level B). Patients should be advised that risk of AED adverse events (AEs) may range from 7% to 31% (Level B) and that these AEs are likely predominantly mild and reversible. Clinicians' recommendations whether to initiate immediate AED treatment after a first seizure should be based on individualized assessments that weigh the risk of recurrence against the AEs of AED therapy, consider educated patient preferences, and advise that immediate treatment will not improve the long-term prognosis for seizure remission but will reduce seizure risk over the subsequent 2 years. *Neurology*® 2015;84:1705-1713

Pharmacology

Review

Pharmacology 2014;93:260–271
DOI: 10.1159/000362419

Received: December 30, 2013
Accepted after revision: March 24, 2014
Published online: August 1, 2014

Advances in Drug Development for Parkinson's Disease: Present Status

Dibbanti Harikrishna Reddy Shubham Misra Bikash Medhi

Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Key Words
Parkinson's disease · Motor disorder · Clinical trials · Phase I · Phase II · Phase III

Abstract
The major hallmark of Parkinson's disease (PD) is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to the characteristic motor symptoms of resting tremors, bradykinesia and rigidity. Research in the field of PD therapy has been partly successful in terms of developing symptomatic treatments, but it also experienced several failures with regard to developing disease-modifying therapies. According to the definition of the Committee to Identify Neuroprotective Agents for Parkinson's, neuroprotection would be any intervention that favorably influences the disease process or underlying pathogenesis to produce enduring benefits for patients. A development of effective neuroprotective therapies resulting in clinically meaningful results is hampered by several factors in all research stages. Novel solutions might be offered by an evaluation of new targets throughout clinical studies, therapies emerging from drug repositioning approaches, multitarget approaches and network pharmacology. Several promising randomized controlled trials are in progress, and the increased collaboration between pharmaceutical companies and basic and clinical researchers has the potential to bring us closer to developing an optimum pharmaceutical approach for the treatment of PD. The aim of the present review is to give an overview of the neuroprotective agents and their targets currently investigated for the treatment of PD in phase I–III clinical trials.

Introduction

Parkinson's disease (PD) is the second most common movement disorder among neurodegenerative diseases [1], first described by James Parkinson in an essay entitled 'An essay on the shaking palsy' in 1817 [2]. Later, the famous French neurologist Jean-Martin Charcot further described the syndrome in the late 1800s. In fact, age is the most important risk factor for PD: worldwide, approximately 1–2% of the population older than 65 years suffer from this slowly progressive degenerative disease [3]. The majority of PD cases are idiopathic (90–95%) with no specific known cause, and the remaining ones are familial forms (5–10%). The genes that are thought to be involved in familial PD are

KARGER

E-Mail karger@karger.com
www.karger.com/pha

0031–7012/14/0936–0260$39.50/0

Dr. Bikash Medhi
Department of Pharmacology
Postgraduate Institute of Medical Education and Research
Chandigarh 160012 (India)
E-Mail drbikashus@yahoo.com

Neurotherapeutics (2014) 11:24–33
DOI 10.1007/s13311-013-0242-1

REVIEW

Therapy for Parkinson's Disease: What is in the Pipeline?

Fabrizio Stocchi

Published online: 17 December 2013

Abstract Despite advances in the treatment of Parkinson's disease there are still many unmet needs, including neuroprotection, treatment of motor complications, treatment of dyskinesia, treatment of psychosis, and treatment of nondopaminergic symptoms. In this review, I highlight the obstacles to develop a neuroprotective drug and some of the treatment strategies recently approved or still in clinical trials designed to meet these unmet needs. nearly all of them failed when tested in clinical trials. For example, a plant-derived substance PYM50028 (Cogane), which promotes expression of endogenous neural growth factors and has shown promise in vitro and in animal models [6], but failed to show improvement in a large phase II trial in early PD when compared with placebo (data on file). Other agents, such as green tea, coenzyme Q10, creatine, GPI-1485, TCH346, CEP1347, and minocycline failed to demonstrate any effect on disease progression.

frontiers in NEUROSCIENCE

REVIEW ARTICLE
published: 22 May 2014
doi: 10.3389/fnins.2014.00113

Advances in non-dopaminergic treatments for Parkinson's disease

Sandy Stayte[1,2] *and Bryce Vissel*[1,2]*

[1] Neuroscience Department, Neurodegenerative Disorders Laboratory, Garvan Institute of Medical Research, Sydney, NSW, Australia
[2] Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia

Edited by:
Eero Vasar, University of Tartu, Estonia

Reviewed by:
Andrew Harkin, Trinity College Dublin, Ireland
Sulev Kõks, University of Tartu, Estonia
Pille Taba, University of Tartu, Estonia
Pekka T. Männistö, University of Helsinki, Finland

**Correspondence:*
Bryce Vissel, Neuroscience Department, Neurodegenerative Disorders Laboratory, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, NSW 2010, Australia
e-mail: brycevissel@gmail.com

Since the 1960's treatments for Parkinson's disease (PD) have traditionally been directed to restore or replace dopamine, with L-Dopa being the gold standard. However, chronic L-Dopa use is associated with debilitating dyskinesias, limiting its effectiveness. This has resulted in extensive efforts to develop new therapies that work in ways other than restoring or replacing dopamine. Here we describe newly emerging non-dopaminergic therapeutic strategies for PD, including drugs targeting adenosine, glutamate, adrenergic, and serotonin receptors, as well as GLP-1 agonists, calcium channel blockers, iron chelators, anti-inflammatories, neurotrophic factors, and gene therapies. We provide a detailed account of their success in animal models and their translation to human clinical trials. We then consider how advances in understanding the mechanisms of PD, genetics, the possibility that PD may consist of multiple disease states, understanding of the etiology of PD in non-dopaminergic regions as well as advances in clinical trial design will be essential for ongoing advances. We conclude that despite the challenges ahead, patients have much cause for optimism that novel therapeutics that offer better disease management and/or which slow disease progression are inevitable.

Keywords: Parkinson's disease, animal models, therapeutics, neurodegeneration, L-Dopa, dyskinesias, dopamine, gene therapy

INTRODUCTION

As the life expectancy in industrialized countries increases, the burden of Parkinson's disease (PD) and the associated economic costs continues to rise, resulting in a dramatic need for effective treatments. Since the 1960's, treatments have been wholly symptomatic, involving a range of approaches to effectively restore, mimic, or replace dopamine (DA). While this treatment strategy, primarily through the use of levodopa (L-Dopa), still remains the most effective method of alleviating the symptoms of PD, its effectiveness is limited as long-term use is associated with the development of debilitating hyperkinetic movements including chorea, dystonia and athetosis, collectively known as L-Dopa-induced dyskinesias (LIDs). It is apparent therefore that the identification of alternative strategies is crucial.

The early success in developing treatment strategies relied on the early understanding that PD is a DA deficiency disorder. However, until recently this concept in many ways also constrained therapeutic development to a strategy of restoring or replacing DA signaling. Studies in rodents and in non-human primates have, however, more recently led to new insights into the mechanisms underlying PD. Such studies, together with some early studies of the effects of brain surgery in humans (Kumar et al., 1998; Burchiel et al., 1999), have been instrumental in subsequently redefining the motor symptoms of PD as the result of an imbalance of excitatory/inhibitory drive in the direct and indirect pathways of the basal ganglia (BG) (Albin et al., 1989, 1995; Graybiel, 1990; Gerfen, 1992; Porter et al., 1994; Wullner et al., 1994; Blandini et al., 2000; Wu et al., 2012) rather than simply resulting from a depletion of DA in the striatum (Dauer and Przedborski, 2003). This in turn has led to a shift in therapeutic development strategies away from DA and toward approaches that work in novel ways to restore the balance of BG signaling (**Figure 1**).

As this review will show, there has been progress. This has resulted in large part due to the ability of animal models to replicate changes in human BG circuits and in turn, provide valuable tools for testing therapies that work to restore the balance of excitatory/inhibitory drive. Animal models of PD have almost exclusively utilized various toxins such as MPTP, 6-OHDA, reserpine

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; DOPAC, 3,4-Dihydroxyphenylacetic acid; 6-OHDA, 6-hydroxydopamine; AIMs, abnormal involuntary movements; AAV, adeno-associated virus; AADC, aromatic l-amino acid decarboxylase; ADAGIO, Attenuation of Disease Progression with Rasagiline Once-daily; BG, basal ganglia; Ca^{2+}, calcium; CNS, central nervous system; CDNF, conserved dopamine neurotrophic factor; COX, cyclooxygenase; DATATOP, Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; DA, dopamine; GDNF, glial derived neurotrophic factor; GPi, globus pallidus internus; GLP-1, glucagon-like peptide 1; GAD, glutamic acid-decarboxylase; HVA, homovanillic acid; LRRK2, lencine-rich repeat kinase-2; LIDs, L-Dopa-induced dyskinesias; LFADLDS, Lang-Fahn Activities of Daily Living Dyskinesia Scale; L-Dopa, LPS, levodopa; lipopolysaccharide; mGluRs, metabotropic glutamate receptors; NMDA, N-methyl-D-aspartate; NTN, neurturin; NSAIDs, non-steroidal anti-inflammatory drugs; NE, norepinephrine; PD, Parkinson's disease; ROS, reactive oxygen species; 5-HT, serotonin; Na^+, sodium; SN, substantia nigra; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; TH, tyrosine hydroxylase; UPDRS, Unified Parkinson's Disease Rating Scale; VMAT2, vesicular monoamine transporter 2.

The Harvard Biomarker Study's big plan

Frustrated by their inability to answer their patients' questions, a team of researcher-clinicians have set up one of the largest biobanks for Parkinson's and Alzheimer's diseases. Their aim? To make personalised medicine a reality. Dara Mohammadi reports.

Published Online
June 26, 2013
http://dx.doi.org/10.1016/
S1474-4422(13)70155-8

For more on the **Harvard Biomarker Study** see http://www.neurodiscovery.harvard.edu/research/biomarkers.html

Clemens Scherzer is caught between centuries. As a researcher-clinician, and one of three co-directors of the Harvard Biomarker Study, he spends much of the time with his eyes firmly on the future—personalised medicine for people with Parkinson's and Alzheimer's diseases. But he is also a practicing neurologist at Brigham and Women's Hospital, MA, and as such has weekly reminders of just how urgent the need for progress is.

"I see Parkinson's patients every Thursday or Friday", he tells *The Lancet Neurology*. "The questions I get pretty much every time I'm in the clinic, and which always make me squirm, are 'Doctor, how am I doing? What's my prognosis for the next few years? Am I responding well to my medicines?' Unfortunately, in Parkinson's we just don't have the answers to any of these questions. It's essentially 19th century medicine."

At present, assessment for Parkinson's disease is based on a physical exam and clinical history, which are then used to monitor disease progression. These assessments are not only unspecific but also highly variable, differing from day to day and from neurologist to neurologist. Alzheimer's disease, too, lacks a simple definitive diagnostic test.

"We want to transform this process from a symptoms-based approach to an approach focused on the molecular disease process", he explains. "The future neurologist will not only do the clinical exam, but will also ask patients for a blood sample, a lumbar puncture, and will run these specimens to assess DNA, RNA expression, and metabolite profiles, and will be able to see the exact molecular disease process of his or her patient."

His interest in this idea was sparked back in 2003, during a number of conversations with Peter Lansbury, a colleague at Brigham and Women's Hospital who 2 years earlier had set up the Laboratory for Drug Discovery in NeuroDegeneration, part of the Harvard NeuroDiscovery Center.

> "'We were talking about finding a cure for Parkinson's", recalls Scherzer, "and the more we tried to figure it out the clearer the answer became."'

"We were talking about finding a cure for Parkinson's", recalls Scherzer, "and the more we tried to figure it out the clearer the answer became." They surmised that even if Lansbury discovered a potential treatment, he would have had to test it on a patient who had only just been clinically diagnosed, at a time when more than 50% of their dopaminergic neurons would have already died.

"At that point in the disease even a good drug is likely not to work in clinical trials—you're just doing too little, too late", he says. It was obvious that the focus on drug discovery alone was not going to cure the disease. What they needed was to focus on a core evolution of drugs and biomarkers. "We had to diagnose earlier, treat earlier, and monitor response to drugs. So then we said: 'OK, what's the solution to this?'"

The solution was the Harvard Biomarker Study, a longitudinal case-control study and biobank that could be trawled for candidate biomarkers. Scherzer "got the ball rolling" the following year by recruiting patients with Parkinson's and healthy controls, but the study didn't take its final shape until 2008, when he joined forces with his two fellow co-directors: Brad Hyman, at Massachusetts General Hospital, and Adrian Ivinson, at Harvard Medical School.

Hyman, an Alzheimer's disease specialist, had also been struggling with his field's inability to confidently provide the answers that his patients were asking. Ivinson is the founding director of the Harvard NeuroDiscovery Center, which pulls together expertise from across the Harvard network to build collaborative, novel neuroscience projects.

And so the Harvard Biomarker Study was born. Their premise was clear: to recruit patients with early-stage Parkinson's or mild cognitive impairment, as well as healthy controls, and to collect an exhaustive set of biosamples—plasma, serum, microRNA, RNA, DNA, whole blood, CSF, immortalised cell lines, and eventually brain autopsies—plus descriptions of the range of clinical phenotypes from as many people as possible.

Once recruited, patients provide biosamples and have detailed

Harvard Medical School in Boston, MA, USA

METABOLISM CLINICAL AND EXPERIMENTAL 64 (2015) 540–546

Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Biomarkers of Parkinson's disease: Present and future

*Diane B. Miller**, James P. O'Callaghan****

Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Morgantown, WV 26505

ARTICLE INFO

Keywords:
Imaging
Fluid biomarkers
α-Synuclein
Transcranial sonography

ABSTRACT

Sporadic or idiopathic Parkinson's disease (PD) is an age-related neurodegenerative disorder of unknown origin that ranks only second behind Alzheimer's disease (AD) in prevalence and its consequent social and economic burden. PD neuropathology is characterized by a selective loss of dopaminergic neurons in the substantia nigra pars compacta; however, more widespread involvement of other CNS structures and peripheral tissues now is widely documented. The onset of molecular and cellular neuropathology of PD likely occurs decades before the onset of the motor symptoms characteristic of PD. The hallmark symptoms of PD, resting tremors, rigidity and postural disabilities, are related to dopamine (DA) deficiency. Current therapies treat these symptoms by replacing or boosting existing DA. All current interventions have limited therapeutic benefit for disease progression because damage likely has progressed over an estimated period of ~5 to 15 years to a loss of 60%–80% of the nigral DA neurons, before symptoms emerge. There is no accepted definitive biomarker of PD. An urgent need exists to develop early diagnostic biomarkers for two reasons: (1) to intervene at the onset of disease and (2) to monitor the progress of therapeutic interventions that may slow or stop the course of the disease. In the context of disease development, one of the promises of personalized medicine is the ability to predict, on an individual basis, factors contributing to the susceptibility for the development of a given disease. Recent advances in our understanding of genetic factors underlying or contributing to PD offer the potential for monitoring susceptibility biomarkers that can be used to identify at-risk individuals and possibly prevent the onset of disease through treatment. Finally, the exposome concept is new in the biomarker discovery arena and it is suggested as a way to move forward in identifying biomarkers of neurological diseases. It is a two-stage scheme involving a first stage of exposome-wide association studies (EWAS) to profile omic features in serum to discover molecular biomarkers. The second stage involves application of this knowledge base in follow-up studies. This strategy is unique in that it promotes the use of data-driven (omic) strategies in interrogating diseased and healthy populations and encourages a movement away from using only reductionist strategies to discover biomarkers of exposure and disease. In this short review we will examine 1) advances in our understanding of the molecular mechanisms underlying PD that have led to candidate biomarkers for diagnosis and treatment efficacy and 2) new technologies on the horizon that will lead to novel approaches in biomarker development.
Published by Elsevier Inc.

* *Correspondence to:* D.B. Miller, Health Effects Laboratory Division, TMBB-HELD, Mailstop L-3014, CDC-NIOSH, 1095 Willowdale Road, Morgantown, WV 26505, USA. Tel.: +1 304 285 5732; fax: +1 304 285 6266.
** *Correspondence to:* J.P. O'Callaghan, Health Effects Laboratory Division, TMBB-HELD, Mailstop L-3014, CDC-NIOSH, 1095 Willowdale Road, Morgantown, WV 26505, USA. Tel.: +1 304 285 6079; fax: +1 304 285 6266.
E-mail addresses: dum6@cdc.gov (D.B. Miller), jdo5@cdc.gov (J.P. O'Callaghan).

http://dx.doi.org/10.1016/j.metabol.2014.10.030

Review

Neuroinflammation in Alzheimer's disease

Michael T Heneka, Monica J Carson, Joseph El Khoury, Gary E Landreth, Frederic Brosseron, Douglas L Feinstein, Andreas H Jacobs, Tony Wyss-Coray, Javier Vitorica, Richard M Ransohoff, Karl Herrup, Sally A Frautschy, Bente Finsen, Guy C Brown, Alexei Verkhratsky, Koji Yamanaka, Jari Koistinaho, Eicke Latz, Annett Halle, Gabor C Petzold, Terrence Town, Dave Morgan, Mari L Shinohara, V Hugh Perry, Clive Holmes, Nicolas G Bazan, David J Brooks, Stéphane Hunot, Bertrand Joseph, Nikolaus Deigendesch, Olga Garaschuk, Erik Boddeke, Charles A Dinarello, John C Breitner, Greg M Cole, Douglas T Golenbock, Markus P Kummer

Lancet Neurol 2015; 14: 388–405

Department of Neurology, University Hospital Bonn, University of Bonn, Bonn, Germany (Prof M T Heneka MD, Prof G C Petzold MD, M P Kummer PhD); German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany (Prof M T Heneka, F Brosseron PhD, Prof E Latz MD,

Increasing evidence suggests that Alzheimer's disease pathogenesis is not restricted to the neuronal compartment, but includes strong interactions with immunological mechanisms in the brain. Misfolded and aggregated proteins bind to pattern recognition receptors on microglia and astroglia, and trigger an innate immune response characterised by release of inflammatory mediators, which contribute to disease progression and severity. Genome-wide analysis suggests that several genes that increase the risk for sporadic Alzheimer's disease encode factors that regulate glial clearance of misfolded proteins and the inflammatory reaction. External factors, including systemic inflammation and obesity, are likely to interfere with immunological processes of the brain and further promote disease progression. Modulation of risk factors and targeting of these immune mechanisms could lead to future therapeutic or preventive strategies for Alzheimer's disease.

LOYOLA MEDICINE

We also treat the human spirit.®