Association of reversed Robin Hood syndrome with risk of stroke recurrence

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ABSTRACT

Background: Reversed Robin Hood syndrome (RRHS) has recently been identified as one of the mechanisms of early neurologic deterioration in acute ischemic stroke (AIS) patients related to arterial blood flow steal from ischemic to nonaffected brain. We sought to investigate the association of RRHS with risk of stroke recurrence in a single-center cohort study.

Methods: Consecutive patients with AIS or TIA affecting the anterior circulation were prospectively evaluated with serial NIH Stroke Scale assessments and bilateral transcranial Doppler monitoring with breath-holding test. RRHS was defined according to previously validated criteria.

Results: A total of 360 patients (51% women, mean age 62 ± 15 years) had an ischemic stroke (81%) or TIA (19%) in the anterior circulation, and 30 (8%) of them had RRHS. During a mean follow-up period of 6 months (range 1–24), a total of 16 (4%) recurrent strokes (15 ischemic and 1 hemorrhagic) were documented. The cumulative recurrence rate was higher in patients with RRHS (19%; 95% confidence interval [CI] 1–37) compared to the rest (15%; 95% CI 0–30; $p = 0.022$ by log-rank test). All recurrent strokes in patients with RRHS were cerebral infarcts that occurred in the ipsilateral to the index event anterior circulation vascular territory. After adjusting for demographic characteristics, vascular risk factors, and secondary prevention therapies, RRHS was independently associated with a higher stroke recurrence risk (hazard ratio 7.31; 95% CI 2.12–25.22; $p = 0.002$).

Conclusions: Patients with AIS and RRHS appear to have a higher risk of recurrent strokes that are of ischemic origin and occur in the same arterial territory distribution to the index event. Further independent validation of this association is required in a multicenter setting. *Neurology*® 2010;75:2003–2008

GLOSSARY

AIS = acute ischemic stroke; **BHI** = breath-holding index; **BP** = blood pressure; **CE** = cardioembolic stroke; **CI** = confidence interval; **HR** = hazard ratio; **ICH** = intracerebral hemorrhage; **IS** = ischemic stroke; **IUC** = infarct of undetermined cause; **LAA** = large artery atherosclerotic stroke; **LAC** = lacunar stroke; **MFV** = mean flow velocity; **MRA** = magnetic resonance angiography; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **RVT** = registered vascular technologists; **RRHS** = reversed Robin Hood syndrome; **SM** = steal magnitude; **TCD** = transcranial Doppler; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment.

The underlying causes of neurologic deterioration in acute ischemic stroke (AIS) patients comprise several different mechanisms including arterial reocclusion, cardiovascular instability, edema progression, and hemorrhagic transformation.[1-5] Real-time monitoring with transcranial Doppler (TCD) may assist in identifying hemodynamic causes of early deterioration.[5-9] One of the mechanisms related to infarct expansion, leading to neurologic deterioration in the setting of acute cerebral ischemia, is an intracranial arterial blood flow steal phenomenon in patients with proximal arterial occlusions.[8,9] More specifically, with hypercapnia, flow velocities paradoxically decrease in the vessels supplying ischemic tissues at the time of velocity increase in the normal arteries, which are able to respond to the carbon dioxide stimulus with a more effective vasodilation. The intracranial steal phenomenon can be quantified by TCD as

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Disclosure: Author disclosures are provided at the end of the article.

mean flow velocity reduction during voluntary breath-holding.[8] If this steal phenomenon leads to neurologic deterioration, the reversed Robin Hood syndrome (RRHS) is diagnosed.[8,9]

The prevalence of intracranial steal phenomenon and RRHS in consecutive patients with acute cerebral ischemia was 14% and 7%.[9] Patients with proximal arterial occlusions and excessive daytime sleepiness appeared particularly vulnerable to the steal that was documented exclusively in the anterior circulation.[9] Furthermore, patients with RRHS tended to have less neurologic improvement at hospital discharge.[9] We hypothesized that this acute and symptomatic hemodynamic compromise could also predispose the patient to a new stroke occurrence. We attempted to evaluate the potential association of RRHS with the risk of stroke recurrence in consecutive patients with acute cerebral ischemia.

METHODS

Study design. Consecutive patients with symptoms of acute anterior cerebral ischemia, admitted within 48 hours from symptoms onset to our tertiary hospital stroke service from November 2007 through December 2009, were prospectively evaluated. Adults with an anterior circulation ischemic stroke (with neuroimaging evidence of acute cerebral infarction in the distribution of anterior circulation) or a TIA, at least 19 years old, with temporal windows for TCD examination, who consented to participate in the study were included. According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, ischemic strokes were classified based on etiopathogenetic mechanisms into the following groups: large artery atherosclerotic stroke (LAA), cardioembolic stroke (CE), small artery occlusion or lacunar stroke (LAC), and infarct of undetermined cause (IUC).[10] Consecutive TCD evaluations were performed on a daily basis during hospitalization to document the presence of reocclusion as a cause of deterioration.

Neurologic deficits were measured by serial NIH Stroke Scale (NIHSS) scores obtained by certified stroke team members. Neurologic deficits were assessed using NIHSS evaluations on a daily basis during hospitalization. Demographics and common risk factors were documented from routine stroke workup as previously described.[8,9]

TCD evaluation. Standard diagnostic TCD and bilateral TCD monitoring with voluntary breath-holding[8,9,11] or during spontaneous apneas[8,9] were performed by registered vascular technologists (RVT), or RVT-eligible sonographers within 24 hours from hospitalization. TCD monitoring of the symptomatic and asymptomatic sides was performed simultaneously (Spencer's ST[3] TCD, Seattle, WA). As an indirect measure of the effectiveness of breath-holding in producing hypercapnia, we used the increase in mean flow velocity (MFV) in the asymptomatic side which was quantified as a breath-holding index (BHI) of >0.69 at the end of breath-holding.[12] If the BHI in the non-affected vessel was ≤ 0.69, the breath-holding procedure was repeated. No case was excluded from the present study on the basis of ineffective breath-holding or absence of spontaneous apneas. We measured the MFV changes during 15–30 seconds of breath-holding.[8] A proximal arterial obstruction was diagnosed when an occlusion or $\geq 70\%$ stenosis of the extracranial ICA, intracranial ICA, or M1 MCA was detected from CT or magnetic resonance angiography (MRA) as previously described.[13-15] The time elapsed between baseline TCD assessment and CTA or MRA was less than 48 hours in all cases. Collaterals on TCD were identified using previously validated criteria.[13-15]

The hemodynamic steal was defined as MFV decrease in the affected vessel at the time of hypercapnia-induced velocity increase in the normal MCA. The vascular steal phenomenon had to occur in the vascular territory considered responsible for the ischemic stroke or TIA for the patient to be classified as having RRHS.[8,9] The steal magnitude (SM, %) was quantified as the maximum negative percent velocity reduction during breath-holding as previously described: $SM = [(MFVm - MFVb)/MFVb] \times 100$, where m = minimum and b = baseline MFVs.[8,9] Steal was considered present when SM was negative, i.e., $SM < 0$ in the affected vessel. After the steal was documented on TCD, RRHS was suspected if new or recurrent neurologic worsening by ≥ 2 NIHSS points was observed without concurrent changes in blood pressure (BP) or arterial patency.[8,9]

Follow-up evaluation. Functional independence at hospital discharge and after a recurrent stroke was evaluated using the modified Rankin Scale (mRS). Patients with mRS score of 0–2 were considered as functionally independent.[16] The secondary prevention therapies were selected by the treating physicians according to the current American Heart Association recommendations and were documented in all cases.[17]

All surviving patients were followed up prospectively at regular intervals after the index event by a study investigator and a trained nurse during the follow-up period. The outcome events of interest were recurrent strokes and deaths. To determine recurrent ischemic stroke (IS) or intracerebral hemorrhage (ICH), we evaluated all the available information obtained from death certificates, hospital records, physicians' notes in private practice, necropsy findings, and the patients' clinical presentation at the regular follow-up assessments. Recurrent stroke was defined as a sudden onset of neurologic deficit that persisted more than 24 hours and clearly resulted in a new neurologic deficit or an increase in an existing deficit.[18] Brain imaging demonstrating a new lesion, involving a different anatomic site or vascular territory from the index event, was mandatory to support the diagnosis of recurrent stroke during the first 3 weeks after stroke onset. The location of cerebral infarctions (anterior vs posterior circulation, ipsilateral vs contralateral to the index ischemic event) was documented in all recurrent ischemic strokes.

Standard protocol approvals, registrations, and patient consents. Our Institutional Review Board approved the present study. We received written informed consent from all patients participating in the study or their guardians.

Statistical analyses. Statistical analyses were performed with the SPSS 15.0 software (SPSS Inc.). The 2-tailed Fisher exact test or Pearson χ^2 test for categorical variables and Student t test or Mann-Whitney U test for continuous variables were used to assess intergroup differences. Data are presented as mean (SD) or as percentages. The Kaplan-Meier product-limit method was used to estimate the cumulative probability of survival and recurrence during the follow-up period from the index event. Kaplan-

Meier curves of groups with and without RRHS are presented and survival free of stroke recurrence is compared between the 2 groups using the log-rank method. To evaluate which factors contribute to long-term recurrence, we performed Cox proportional hazards analyses. Those factors that contributed to the outcome in the initial univariate analyses at $p < 0.2$ (because of the risk of type II error due to low statistical power in such an analysis) were included in the multivariate model as candidate variables. The final variables that were independently associated in the multivariate analyses with stroke recurrence were selected by forward stepwise selection procedure using a p value <0.05. To confirm the robustness of multivariate models, we also performed all multivariate analyses using a backward-selection procedure. Associations are presented as hazard ratios (HR) with corresponding 95% confidence intervals (95% CI).

RESULTS A total of 360 of the 581 patients admitted to our stroke service during the study period (51% women, mean age 62 ± 15 years; 81% AIS, 19% TIA) fulfilled our inclusion criteria. Twelve patients were unable to perform voluntary breath-holding and the presence of intracranial steal phenomenon was identified during spontaneous apneas. RRHS was identified in 30 cases (8%, 29 during voluntary breath-holding and 1 during spontaneous apneas). Demographic characteristics, vascular risk factors, and secondary prevention therapies of the study population are shown in table 1. Male gender was more common in RRHS patients (77% vs 47%; $p = 0.002$). RRHS was more prevalent in white subjects (11%) compared with African American subjects (4%; $p = 0.031$). The underlying stroke pathogenic mechanism was LAA in 67% of patients with RRHS and in 28% of those without RRHS ($p < 0.0001$). In addition, patients with RRHS had a higher prevalence of proximal arterial obstruction (93% vs 26%, $p < 0.0001$). Patients with RRHS tended to have lower functional independence rates at hospital discharge (43% vs 58%; $p = 0.124$).

Table 1 Baseline characteristics of the study population (n = 360)[a]

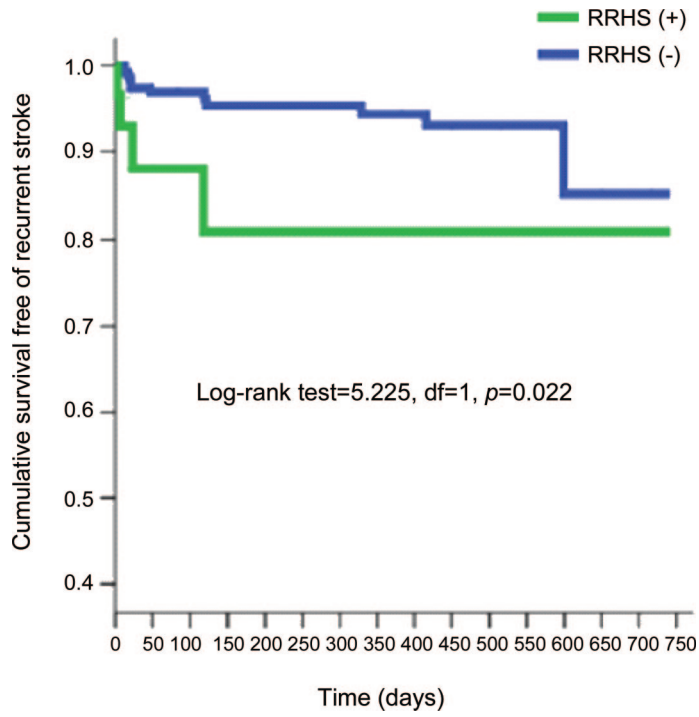
Variable	Value
Age, y, mean (SD)	62 (15)
Male gender	178 (49)
African American ethnicity	138 (38)
Acute ischemic stroke	290 (81)
Transient ischemic attack	70 (19)
Stroke severity on admission: NIH Stroke Scale score, median (interquartile range)	4 (9)
Large-artery atherosclerotic stroke	111 (31)
Proximal arterial obstruction	115 (32)
Hypertension	316 (88)
Diabetes mellitus	142 (39)
Coronary artery disease	118 (33)
Atrial fibrillation	68 (19)
Smoking	163 (65)
Hypercholesterolemia	283 (79)
Aspirin at hospital discharge	172 (48)
Other antiplatelet at hospital discharge	145 (40)
Oral anticoagulants at hospital discharge	43 (12)
Lipid-lowering medication at hospital discharge	318 (88)
Blood-pressure lowering medication at hospital discharge	316 (88)

[a] Values are n (%) unless otherwise indicated.

During a mean follow-up period of 6 months (range 1–24), a total of 16 (4%) recurrent strokes (15 ischemic and 1 hemorrhagic) were documented. The duration of follow-up period was similar between patients with RRHS (6.6 ± 8.2 months) and patients without TCD evidence of intracranial steal phenomenon (6.0 ± 7.2 months; $p = 0.653$). Four out of the 16 (25%) recurrent strokes were fatal. The cumulative recurrence rate was higher in patients with RRHS (19%; 95% CI 1–37) compared to the rest (15%; 95% CI 0–30; $p = 0.022$ by log-rank test; figure). All recurrent strokes in patients with RRHS were cerebral infarcts in the anterior circulation vascular territory ipsilateral to the index event. The mean elapsed time between the index and the recurrent stroke tended to be shorter in patients with RRHS (1.2 ± 1.8 months) compared to the rest (4.7 ± 6.4 months; $p = 0.110$). The 1-month stroke recurrence rate was 4-fold higher in RRHS (12%; 95% CI 0–25) compared to the rest (3%; 95% CI 1–5; $p = 0.015$ by log-rank test). Factors associated with a higher risk of stroke recurrence in the univariate and multivariate Cox regression models are shown in table 2. In the initial univariate analyses, the following factors were selected for inclusion in the multivariate model: RRHS, age, coronary artery disease, and AIS (vs TIA). In the final multivariate analyses (performed by forward selection procedure), RRHS, age, and coronary artery disease were independently related to the risk of stroke recurrence. The presence of RRHS was independently associated with a higher risk of stroke recurrence (HR 7.31; 95% CI 2.12–25.22; $p = 0.002$). After performing the multivariate analyses using a backward selection procedure, we obtained practically identical results regarding the relationship of RRHS with risk of stroke recurrence (HR 5.90; 95% CI 1.70–20.22; $p = 0.005$).

We also excluded patients who were unable to perform voluntary breath-holding (n = 12) and repeated our analyses. RRHS was independently associated with a higher risk of stroke recurrence (HR 12.45; 95% CI 2.78–55.68; $p = 0.001$). Since the number of outcome events was low (n = 16), the maximum number of predictor variables that should

Figure Kaplan-Meier curves of patients with and without reversed Robin Hood syndrome (RRHS) surviving free from recurrent stroke from time of index event



be included in the multivariate model would be 2. If a more stringent cutoff was used in the univariate analyses ($p < 0.150$), then only RRHS ($p = 0.032$) and coronary artery disease ($p = 0.116$) would be eligible for inclusion in the multivariate model [age ($p = 0.165$) and AIS ($p = 0.198$) would be excluded from the final model]. In this case, the association between RRHS and risk of stroke recurrence would be attenuated (HR 4.54; 95% CI 1.43–14.39; $p = 0.010$).

During the follow-up period, 33 patients died (9%). The cumulative survival rate was similar in patients with RRHS (84%; 95% CI 66–100) compared to the rest (85%; 95% CI 78–82; $p = 0.947$ by log-rank test). On univariate Cox regression models, RRHS was not associated with a higher risk of death (HR 1.04; 95% CI 0.32–3.41; $p = 0.947$).

DISCUSSION Our study showed that patients with acute anterior circulation ischemic events and RRHS have a significantly higher risk of new ischemic stroke occurrence during follow-up than acute stroke patients without this condition. This longitudinal association persisted even after adjustment for demographic characteristics, vascular risk factors, and secondary prevention therapies. We also observed that all recurrent strokes in the RRHS subgroup occurred in the anterior circulation vascular territory ipsilateral to the index event. A trend for earlier recurrent strokes was also noted in the RRHS group (75% of recurrent strokes occurred during the first month).

Our study confirmed the previously reported prevalence of RRHS among patients with AIS or TIA and their demographic characteristics (white men were predominant in this specific population).[9] We also corroborated the previously observed significant association between RRHS and proximal arterial obstruction,[8,9] as well as the higher prevalence of large vessels disease as underlying pathogenetic mechanism in patients with RRHS, although it should be noted that 11 out of the 30 patients with RRHS were included in the previous publication from our group.[9] Patients with LAA stroke have a higher risk of recurrent stroke compared to other AIS subtypes,[19] while intracranial arterial occlusions or hemodynamically significant stenoses (>70%) also carried a substantial risk of stroke recurrence.[20] Interestingly, in our series the relationship of RRHS with higher incidence of stroke recurrence persisted even after adjustment for TOAST subtype and the presence of proximal arterial obstruction. This finding indicates that the hemodynamic compromise caused by the vascular steal phenomenon may be an underlying mechanism linking large vessel atherosclerosis both with neurologic deterioration in the acute stroke setting as well as with recurrent cerebral ischemia during the first months after the index. The fact that all recurrent strokes in RRHS subgroup occurred in the same anterior circulation vascular territory, with the majority taking place during the first month of ictus, is consistent with the former hypothesis. However, it should be noted that given the relatively small sample size of outcome events (n = 16), the present observation might only be valid for hypothesis generation and require independent validation from other groups.

To our knowledge, the potential association between RRHS and recurrent stroke had not been previously evaluated either in a cross-sectional or in a longitudinal fashion. The high cumulative stroke recurrence, both during the first month (12%) and during a mean follow-up period of 6 months (19%), may raise certain potential clinical implications. Given the noninvasive nature of TCD, the short time required to document this vascular steal phenomenon during voluntary breath-holding, and the satisfactory interobserver agreement for TCD diagnosis of RRHS among experienced sonographers (Cohen $\kappa = 0.89$),[9] RRHS may constitute an easily identifiable cause of neurologic deterioration and early stroke recurrence among patients with acute cerebral ischemia. Furthermore, in our previous studies we observed an association between RRHS and the likelihood

Table 2 Univariate and multivariate Cox proportional hazard analyses determining the effect of different factors on recurrence

	Univariate analysis		Multivariate analysis[a]	
Dependent variable: baseline characteristics	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Age (per 10-year increase)	1.27 (0.91–1.78)	0.165	1.49 (1.06–2.10)	0.021
Male gender	1.37 (0.51–3.67)	0.534		
African American ethnicity	1.53 (0.58–4.08)	0.393		
Hypertension	23.83 (0.02–33,051.89)	0.390		
Diabetes mellitus	1.18 (0.44–3.16)	0.750		
Hypercholesterolemia	0.72 (0.23–2.27)	0.576		
Smoking	1.20 (0.45–3.20)	0.719		
Coronary artery disease	0.30 (0.07–1.34)	0.116	0.18 (0.04–0.83)	0.028
Atrial fibrillation	1.81 (0.63–5.26)	0.273		
AIS vs TIA	29.52 (0.17–5,093.12)	0.198		
Admission NIHSS (per 1-point increase)	1.03 (0.96–1.10)	0.397		
Large artery atherosclerotic stroke	1.02 (0.35–2.93)	0.977		
Proximal arterial obstruction	1.21 (0.44–3.32)	0.717		
RRHS	3.46 (1.11–10.76)	0.032	7.31 (2.12–25.22)	0.002
Antihypertensive medications[b]	23.83 (0.02–33,051.89)	0.390		
Lipid-lowering medications[b]	0.58 (0.22–1.54)	0.272		
Aspirin (vs other antiplatelet agent)[b]	0.87 (0.33–2.32)	0.783		
Oral anticoagulants[b]	0.48 (0.06–3.62)	0.474		

Abbreviations: AIS = acute ischemic stroke; CI = confidence interval; NIHSS = NIH Stroke Scale score; RRHS = reversed Robin Hood syndrome.
[a] Forward selection procedure.
[b] At hospital discharge.

of obstructive sleep apnea and we noted neurologic improvement when patients with obstructive sleep apnea syndrome and RRHS were placed on biphasic positive airway pressure treatment.[8,9] We hypothesized that changes in blood carbon dioxide concentration in AIS with hemodynamic impairment may represent the missing link between stroke recurrence and obstructive sleep apnea.[8,9] The present study findings in combination with our former observations motivate us to formally investigate this intriguing hypothesis in a future study using early hemodynamic assessment of collateral flow, monitoring of respiratory function, and formal sleep study in AIS patients. If we provide additional evidence confirming that hypercapnia is indeed inducing the steal phenomenon in AIS with obstructive sleep apnea, which in turn causes neurologic deterioration and early stroke recurrence, this may open a novel promising technological venue to further explore noninvasive ventilatory correction in this specific stroke subgroup in terms of reduction of recurrent stroke.[21,22]

Our study has certain limitations that need to be acknowledged. First and most important, both the duration of the follow-up period and the number of outcome events were limited. Because this was a single-center study, a type II error may not be excluded. This is the reason we chose to select a univariate p value of <0.2 as a cutoff for inclusion of predictor variables in the final multivariable model. However, it should be noted that the maximum number of predictor variables that should be included in the multivariate models should be 2 given the limited number of outcome events (n = 16). On the other hand, it is worth mentioning that when we applied a more stringent cutoff in the univariate analyses ($p < 0.150$), only 2 variables were included in the multivariable model, while the association of RRHS with higher risk of recurrent stroke despite being attenuated retained its significance ($p = 0.010$). Second, we used a single short-duration ultrasound test that provides only a snapshot and does not answer the question of what happens to the steal over time. Moreover, a subgroup of patients (n = 12) was unable to perform voluntary breath-holding and in these patients the presence of steal phenomenon was documented during spontaneous apneas.[8] This issue may have biased the reported associations, although it is noteworthy that the association between RRHS and higher risk of stroke recurrence persisted even after exclusion of noncompliant patients.

Third, TCD may reliably detect this vascular steal only in proximal anterior circulation vessels (continuous TCD monitoring of intracranial arteries at a steady angle of insonation can be achieved only via the transtemporal window using a headframe),[8,9] and, therefore, we may have missed the presence of RRHS in more distal anterior circulation vessels (e.g., M3MCA) as well as the posterior circulation. Patient evaluation by simultaneous use of other techniques able to investigate cerebral hemodynamics distally (e.g., near infrared spectroscopy)[23] may enable us to address this issue in the future. Fourth, we performed no monitoring of respiratory function, and subsequently, we are unable to evaluate a potential relationship between hypercapnia and stroke recurrence. Fifth, our ultrasonographic criteria for RRHS may be technically challenging for inexperienced sonographers. In view of the former methodologic shortcomings, we consider that our findings regarding the association of RRHS with higher risk of recurrent stroke should be cautiously interpreted and replicated in a larger series of patients by other independent investigators using both ultrasound and other neuroimaging modalities (e.g., single photon emission computed tomography)[23] for vasomotor reactivity assessment. Sixth, in patients with persisting arterial occlusions, the sluggish flow may impair the washout of emboli and thus it may be postulated that artery-to-artery embolization may also contribute to

the documented association between RRHS and recurrent stroke. Unfortunately, formal emboli monitoring (lasting at least 1 hour) was not performed in our dataset and we plan to evaluate this timely issue (artery-to-artery embolism in patients with proximal arterial occlusions and RRHS) in a future study.

DISCLOSURE

Dr. Palazzo completed Stroke Research and Neurosonology Fellowship at UAB funded by Università Campus Bio-Medico, Rome, Italy. Dr. Balucani, Dr. Barlinn, Dr. Tsivgoulis, Dr. Zhang, and Dr. Zhao report no disclosures. Dr. DeWolfe serves on speakers' bureaus for and has received funding for travel and speaker honoraria from UCB and GlaxoSmithKline; and receives research support from UCB and Marinus Pharmaceuticals, Inc. Dr. Toaldo, Dr. Stamboulis, Dr. Vernieri, Dr. Rossini, and Dr. Alexandrov report no disclosures.

Received May 26, 2010. Accepted in final form August 18, 2010.

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