Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies

In the article "Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies," Jalini et al. reported atrial cardiopathy in 26.6% of patients meeting the criteria for embolic stroke of unknown source (ESUS) vs 12.1% of patients with large artery atherosclerosis and 16.9% of those with small vessel disease in a cross-sectional study of 846 consecutive patients with ischemic stroke. They also found that patients with ESUS were younger, less hypertensive, and had higher cholesterol and low-density protein levels but fewer left ventricular or atrial abnormalities compared with yet another group with cardioembolism. In response, Drs. Lattanzi and Silvestrini note that they recently found an inverse association between abnormally increased P-wave terminal force in lead V1 (a marker of atrial cardiopathy) and paradoxical or artery-to-artery embolic sources in patients with ESUS. Patients with anterior circulation ESUS more often had ipsilateral (vs contralateral) internal carotid artery plaques with more concerning atherosclerotic findings, whereas younger patients with ESUS had higher incidence of patent foramen ovale (PFO) and lower rates of other vascular risk factors or markers of cardiopathy or atherosclerosis. Stating that ESUS is thus a heterogeneous entity, they encourage the identification of such distinct phenotypes to help guide secondary prevention and potentially targeted interventions. In their reply, the authors agree that the ESUS definition seems too broad and that factors such as PFO, aortic arch, and nonstenotic carotid plaques that were not addressed in their study are important embolic sources in subgroups of patients with ESUS. They note that ongoing trials in subgroups of patients with ESUS will further inform secondary prevention in this population.

Aravind Ganesh, MD, DPhil, and Steven Galetta, MD
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Reader response: Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies

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We read with great interest the article by Jalini et al.,[1] which demonstrated a higher prevalence of atrial cardiopathy in patients with embolic strokes of undetermined source (ESUS) compared with patients with large artery and small vessel disease strokes.

We recently found that abnormally increased P-wave terminal force in lead V1 in patients with ESUS was inversely associated with paradoxical and artery-to-artery embolic sources, including patent foramen ovale (PFO) and vulnerable, unstable substenotic atherosclerotic plaques of aortic arch and neck arteries.[2] In patients with anterior circulation ESUS, internal carotid artery plaques with increased thickness, mobility, ulceration, and low or heterogeneous echo were more common when ipsilateral rather than contralateral to the stroke site.[3] Younger patients with

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ESUS had lower rates of vascular risk factors, left atrial enlargement, and ventricle dysfunction, but higher incidence of PFO, and no atherosclerosis.[4]

The comprehensive analysis of these alternative causes or putative indicators of embolism according to the presence of atrial cardiopathy would have enhanced the causal link between atrial cardiopathy and stroke occurrence. Far from being a homogeneous entity, the ESUS include a variety of etiologies. The identification of distinct phenotypes on the basis of the underlying pathogenesis could have a great influence in targeting interventions and improving secondary prevention.[5]

1. Jalini S, Rajalingam R, Nisenbaum R, et al. Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies. Neurology Epub 2018 Dec 5.
2. Lattanzi S, Cagnetti C, Pulcini A, et al. The P-wave terminal force in embolic strokes of undetermined source. J Neurol Sci 2017;375:175–178.
3. Komatsu T, Iguchi Y, Arai A, et al. Large but nonstenotic carotid artery plaque in patients with a history of embolic stroke of undetermined source. Stroke 2018;49:3054–3056.
4. Piffer S, Bignamini V, Rozzanigo U, et al. Different clinical phenotypes of embolic stroke of undetermined source: a subgroup analysis of 86 patients. J Stroke Cerebrovasc Dis 2018;27:3578–3586.
5. Lattanzi S, Brigo F, Cagnetti C, Di Napoli M, Silvestrini M. Patent foramen ovale and cryptogenic stroke or transient ischemic attack: to close or not to close? A systematic review and meta-analysis. Cerebrovasc Dis 2018;45:193–203.

Author response: Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies

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We thank Drs. Lattanzi and Silvestrini for their interest in our article.[1] We agree that the current definition of embolic stroke of undetermined source (ESUS) seems too broad and that although we did not address these groups in our study, factors such as PFO, aortic arch, and nonstenotic carotid plaques are important sources of emboli in subpopulations of patients with ESUS. As we have learned repeatedly in stroke research, clinical constructs evolve, and appropriate patient selection can be the key to potentially unmasking therapeutic strategies. We look forward to the results of trials assessing the optimal secondary prevention strategies in subgroups of patients with ESUS.[2,3]

1. Jalini S, Rajalingam R, Nisenbaum R, et al. Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies. Neurology 2019;92:e288–e294.
2. Geisler T, Poli S, Meisner C, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): rationale and study design. Int J Stroke 2017;12:985–990.
3. Kamel H, Longstreth WT Jr, Tirschwell DL, et al. The AtRial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke randomized trial: rationale and methods. Int J Stroke 2019;14:207–214.

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Editors' note: Adherence with psychotherapy and treatment outcomes for psychogenic nonepileptic seizures

In the article "Adherence with psychotherapy and treatment outcomes for psychogenic nonepileptic seizures," Tolchin et al. reported that among 105 participants with documented psychogenic nonepileptic seizures (PNES), adherence with psychotherapy was associated with reduction in PNES frequency, improvement in quality of life, and decrease in emergency department visits at 12–24 months of follow-up. In response, Dr. Sethi notes that psychiatrists and psychologists may be reticent to accept care for patients with PNES when neurologists do not equivocally confirm the diagnosis. He encourages neurologists to sincerely attempt to rule in or rule out coexisting epilepsy in such cases. In their reply, the authors agree that making a definitive diagnosis is possible and that clear communication to both patients and behavioral specialists is essential to facilitate appropriate treatment and adherence. They emphasize the importance of capturing all typical spells on video-electroencephalography and suggest that neurologists review previous EEGs when there is suspicion that a previous "abnormal" EEG may have been overread to avoid clouding an otherwise clear diagnosis of PNES. Dr. Benbadis, who wrote the accompanying editorial for the article, responds in agreement with Dr. Sethi and like the authors notes that only 10%–15% of patients with PNES truly have evidence of coexisting epilepsy. He suggests that including "psychogenic" in the diagnosis is critical, unless there is doubt that there is another nonepileptic diagnosis. He wonders whether mental health professionals may not believe the diagnosis. In addition to encouraging tracking down previous EEGs of concern, he also argues that coexisting epilepsy should not be a reason to deny patients with PNES access to treatment by psychiatrists and psychologists.

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Reader response: Adherence with psychotherapy and treatment outcomes for psychogenic nonepileptic seizures

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I read with interest the article by Tolchin et al. and the accompanying editorial by Dr. Benbadis.[1,2] One reason why psychiatrists and psychologists resist accepting the care of patients with psychogenic nonepileptic seizures (PNES) is the failure of the diagnosing neurologist to confirm the diagnosis unequivocally. Many times, we, as epileptologists, are guilty of saying that the patient has PNES, but—because an EEG in the remote past was read as abnormal—a seizure disorder cannot be ruled out. This creates a diagnostic conundrum and treatment dilemma for both the patient and the psychiatrist. Whenever a diagnosis of PNES is made, we—as neurologists—should make a sincere attempt to rule out or rule in coexisting seizure disorder.

1. Tolchin B, Dworetzky BA, Martino S, Blumenfeld H, Hirsch LJ, Baslet G. Adherence with psychotherapy and treatment outcomes with psychogenic nonepileptic seizures. Neurology 2019;92:e675–e679.
2. Benbadis SR. Psychogenic nonepileptic seizures, conversion, and somatic symptom disorders. Neurology 2019;92:311–312.

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Author response: Adherence with psychotherapy and treatment outcomes for psychogenic nonepileptic seizures

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We appreciate Dr. Sethi's important reminder that it is the responsibility of neurologists to diagnose both psychogenic nonepileptic seizures (PNES) and epilepsy and—in cases of PNES—to rule out or rule in comorbid epilepsy. Making as definite a diagnosis is possible and communicating the diagnosis clearly to the patient and to the treating behavioral specialists is essential to the treatment of PNES. An ambiguous diagnosis can undermine the confidence of the patient and behavioral health specialists in the psychotherapeutic process, leading to nonadherence.

This is why it is important, whenever possible, to capture all typical spells on video EEG during spell characterization, as recommended by the International League Against Epilepsy Nonepileptic Seizures Task Force.[1,2] In addition, in situations like those described by Dr. Sethi, in which a previous EEG was read as abnormal, we recommend that the current neurologist obtain and review the original EEG, as normal EEG activity is frequently overread as epileptiform abnormalities.[3] Although comorbid PNES plus epilepsy does exist in a small minority of cases, it is not the common occurrence that older research suggested.[4] It is important that a previous overread EEG not be allowed to confuse an otherwise clear diagnosis of PNES and thereby undermine treatment.

1. Tolchin B, Dworetzky BA, Martino S, Blumenfeld H, Hirsch LJ, Baslet G. Adherence with psychotherapy and treatment outcomes with psychogenic nonepileptic seizures. Neurology Epub 2019 Jan 4.
2. LaFrance WC Jr, Baker GA, Duncan R, Goldstein LH, Reuber M. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach: a report from the International League Against Epilepsy Nonepileptic Seizures Task Force. Epilepsia 2013; 54:2005–2018.
3. Benbadis SR. "Just like EKGs!" Should EEGs undergo a confirmatory interpretation by a clinical neurophysiologist? Neurology 2013;80: S47–S51.
4. Kutlubaev MA, Xu Y, Hackett ML, Stone J. Dual diagnosis of epilepsy and psychogenic nonepileptic seizures: systematic review and meta-analysis of frequency, correlates, and outcomes. Epilepsy Behav 2018;89:70–78.

Editorialist response: Adherence with psychotherapy and treatment outcomes for psychogenic nonepileptic seizures

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I completely agree with Dr. Sethi that the diagnosis, once made, should be given unequivocally. The diagnosis of psychogenic nonepileptic seizures (PNES) can be challenging at times, but is straightforward most of the time. Similarly, and contrary to higher percentages that are often brought up, only 10%–15% of patients with PNES have evidence for coexisting epilepsy. That means over 85% do not; so, systemically assuming that the patient also has epilepsy is not based on facts. Also vague terms, such as nonepileptic seizures (NES), and ambiguity should be avoided. The "P" is critical. NES and PNES are not the same. Not everything that is nonepileptic is psychogenic. When in doubt, patients should not be labeled psychogenic.

Epilepsy centers always try to rule out coexisting epilepsy. But even if we performed EEG-video monitoring for 6 months, we could not guarantee that the patient will not have an epileptic

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seizure in the seventh month. The concern about coexisting epilepsy may be one reason psychiatrists and psychologists do not want to see those patients, but it is not the main one. I submit that even in patients with unequivocal obvious PNES and no evidence for coexisting epilepsy whatsoever, it is difficult to get them to see psychiatrists and psychologists. More than a concern about coexisting epilepsy, the issue may be that mental health professionals do not believe the diagnosis; worse, some mental health professionals may not believe in the diagnosis of somatic symptom disorders. The issue of a previous EEG that was (mis)read as "showing epilepsy" is frustrating; we must try to obtain the record in question, but that can be difficult. Last, even the 10%–15% of patients with PNES who do have coexisting epilepsy deserve to be treated by psychiatrists and psychologists. That should not be a reason to deny them treatment.

CORRECTIONS

Biallelic variants in *LARS2* and *KARS* cause deafness and (ovario)leukodystrophy

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In the article "Biallelic variants in *LARS2* and *KARS* cause deafness and (ovario)leukodystrophy" by van der Knaap et al.,[1] first published online ahead of print February 8, 2019, the label for the purple marker in figure 3 should read "Hearing loss/Leukodystrophy." The corrected figure appears in the March 12 issue. The publisher regrets the error.

Reference

1. van der Knaap MS, Bugiani M, Mendes MI, et al. Biallelic variants in *LARS2* and *KARS* cause deafness and (ovario)leukodystrophy. Neurology 2019:92:e1225–e1237.

Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors

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In the article "Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors" by Harden et al.,[1] the correct value of the lower limit in the confidence interval for the odds ratio of presence of generalized tonic-clonic seizure (GTCS) vs lack of GTCS shown in table 2 is 7. The authors regret the error.

Reference

1. Harden C, Tomson T, Gloss D, et al. Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors. Neurology 2017;88:1674–1680.

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Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors

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