Diltiazem-induced myoclonus

To the Editor: In the report by Vadlamudi and Wijdicks on verapamil-induced myoclonus,[1] the authors omit diltiazem from their table of drugs that cause myoclonus. Diltiazem has been found to cause reversible myoclonus, even at therapeutic doses.[2] Although their patients overdosed on a calcium-channel blocker, it should be stressed that this class of medications can cause myoclonus even at therapeutic doses.

Joseph S. Jeret, MD, *Rockville Centre, NY*

Reply from the Authors: No table pretends to be all inclusive, but we assume that if myoclonus is seen in one calcium-channel blocker, it likely will be seen in other calcium-channel blockers as well. Dr. Jeret's observation in two patients with episodic myoclonus but without evidence of toxicity is quite helpful.

Eelco F.M. Wijdicks, MD, *Rochester, MN*

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The pulvinar sign and diagnosis of Creutzfeldt-Jakob disease

To the Editor: Haïk et al. present a case report of a patient with histologically confirmed sporadic Creutzfeldt-Jakob disease (sCJD) with bilateral increased signal in the pulvinar of the thalamus.[1] We felt it important to clarify recent changes in the definition of the pulvinar sign to avoid difficulties in future diagnosis of variant CJD (vCJD) using MRI.

The presence of pulvinar hyperintensity was originally described as a characteristic feature of vCJD by Sellar et al.[2] in 1997, and the high sensitivity and specificity of this sign were subsequently documented by our group.[3] Clinical criteria for a diagnosis of vCJD were formulated that incorporated these MRI findings with diagnostic changes defined as bilateral pulvinar high signal on MRI scan.[4] It has been recognized that this definition was ambiguous, as it was unclear with which structure the degree of pulvinar hyperintensity was compared.

Recently, a more specific definition of the pulvinar sign has been developed and included in the recently published World Health Organization (WHO) revised case definition of vCJD.[5] The new definition of the pulvinar sign in vCJD is bilateral symmetrical pulvinar high signal *relative to the signal intensity of other deep grey matter nuclei and cortical grey matter.* This definition emphasizes that, for the sign to be considered positive, the *highest* signal of grey matter is within the pulvinar of the thalamus in vCJD; this does not exclude some increase in signal in other grey matter structures. Recent analysis by our group of MRI scans of patients with definite vCJD has shown that the sensitivity of the pulvinar sign for a diagnosis of vCJD remains very high and in fact has increased with the wider use of fluid-attenuated inversion recovery imaging and with improvements of MRI scanner technology.

There is considerable overlap in the appearances of grey matter structures in different forms of CJD. However, to date the pulvinar sign (as defined in the WHO criteria) remains a robust, sensitive, and highly specific noninvasive diagnostic sign of vCJD that has not been reported in other forms of CJD. The imaging appearances correlate with extensive neuronal loss and gliosis within the pulvinar on neuropathologic studies,[3] changes that have not been reported in other forms of CJD.

We have encountered several cases where a false-positive diagnosis of vCJD has been suggested by radiologists and clinicians that are not experienced in the diagnosis of this form of the disease. We hope the improved definition of the pulvinar sign of vCJD will reduce the number of these cases and are happy to provide a second opinion of MRI scans in which the diagnosis is suspected clinically but interpretation of the scan is considered difficult.

D.M. Summers, MD, D.A. Collie, MD, R.J. Sellar, MD, M. Zeidler, MD, R. Knight, MD, R.G. Will, MD, J.W. Ironside, MD, *Edinburgh, Scotland, UK*

Reply from the Authors: We thank Summers et al. for their useful comments on our report about the specificity of the pulvinar sign for the diagnosis of vCJD *versus* sCJD. They emphasize the importance of the recent revision of the vCJD case definition illustrated by the case that we reported. In this sCJD case, there was a confusing clinical course, neuropathologic lesions, and increased signal on MRI in the pulvinar. However, the signal of the putamen was higher than the pulvinar signal in a T2-weighted sequence and diffusion-weighted images. Thus, the pulvinar high signal in this case could not be considered as a genuine pulvinar sign.[3,5] We agree that the first definition of MRI findings in the clinical criteria for the diagnosis of vCJD[4] was ambiguous, as illustrated by our report, and that MRI pattern of vCJD and sCJD can share signal abnormalities, especially in the deep grey matter. Therefore, it was necessary to clarify the MRI criteria for the diagnosis of vCJD. A more precise definition is now available[5] and in agreement with our conclusion.[1] We hope that our report and the comments of Summers et al. can facilitate the difficult MRI approach of vCJD diagnosis.

S. Haïk, MD, J.P. Brandel, MD, C. Oppenheim, MD, V. Sazdovitch, MD, D. Dormont, MD, J.J. Hauw, MD, C. Marsault, MD, *Paris, France*

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Economy class stroke syndrome

To the Editor: Isayev et al.[1] describe three cases of ischemic stroke in young adults that occurred during or after air travel. All patients were diagnosed with persistent foramen ovale (PFO), and no other plausible cause of stroke could be found, suggesting the existence of an "economy class stroke syndrome." To underscore the importance of their report, we would like to add three very similar patients (aged 21, 63, and 64 years) with otherwise unexplained ischemic strokes that occurred during long-distance air travel (> 9000 km in each case) who were admitted to our department within the past year. All patients developed their symptoms toward the end of their flights, one patient immediately after a prolonged defecation with repeated Valsalva maneuvers. All in-

farcts appeared embolic upon brain imaging. They were located in the right middle cerebral artery territory in one patient and in the posterior thalamus with transient "top of the basilar" syndrome in another. The third patient had multiple embolic cerebral infarctions accompanied by fulminant pulmonary embolism. The latter patient carried a homozygote prothrombin gene G20210a mutation and subsequently died due to cerebral herniation. The other two patients recovered with no or minimal residual deficits. All patients had a PFO as demonstrated by transesophageal echocardiography; one patient had an additional intraseptal aneurysm. Similar to the patients reported by Isayev et al.,[1] lower limb venous Doppler performed within 1 to 3 days after the events was negative in all three cases, as were their extracranial and intracranial Doppler/duplex examinations, ECG-holter recordings, and all other coagulation studies (antithrombin, factor V Leiden mutation, anticardiolipin antibodies, lupus anticoagulant, proteins C and S). Although two of our patients were already in their 60s, none showed evidence of atherosclerosis or other cardiovascular risk factors.

Of course, owing to the worldwide increase in air travel, more people will suffer a stroke in flight by mere chance. Nevertheless, we also assume that embolic strokes during or due to long-distance air travel have been underreported in the literature, but one more patient was reported a few years ago in a French journal.[2] Until more systematic investigations become available, ischemic stroke should be included in the list of potential complications of long-distance air travel, especially in the presence of PFO.

Christian Foerch, Kirn R. Kessler, Helmuth Steinmetz, and Matthias Sitzer, *Frankfurt am Main, Germany*

Reply from the Authors: We thank Foerch et al. for their comment and for bringing to our attention the article by Masson et al.[2] Similar to the three cases we reported, the strokes reported by Foerch et al., appear to be related to prolonged air travel. Their cases were related to flights of about 10 hours or more. Although longer duration flights have a higher risk of pulmonary embolism and probably also of stroke, our cases suggest that stroke can be related to shorter duration flights as well. An important similarity to our experience is that the three cases reported by Foerch et al. were collected from a single center within a very short period of time. This suggests that the "economy class" stroke syndrome is probably not rare, particularly with current high volumes of intercontinental flights.

Richard K. Chan, MBBS, FRCP (Edin), Patrick Pullicino, MD, Ph.D, *Newark, NJ*

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Manometry combined with cervical puncture in idiopathic intracranial hypertension

To the Editor: We agree with King et al.[1] that there is a relationship between intracranial pressure and sinus venous pressure. We do, however, have concerns over the authors' conclusion that increased cerebral venous pressure found in most patients with isolated intracranial hypertension (IIH) is due to a functional obstruction (collapse of the walls) of the transverse sinuses (TS) by raised intracranial pressure and not due to a primary obstructive process in the TS.

We recently demonstrated on MR venography (MRV) that a number of subjects with IIH with or without papilledema had flowing abnormalities of both transverse sinuses, which is highly suggestive of cerebral venous thrombosis.[2,3] It is noteworthy that the flowing abnormalities seen on MRV in IIH occurred mainly in the distal portion of the TS.[2,3] This observation was confirmed by King et al.,[1] who showed a pressure gradient between the proximal and distal part of the TS in patients with IIH. These findings suggest there must be some anatomic reason that makes the distal part of the transverse sinus the preferential site for developing an obstructive process. Because arachnoidal granulations typically occur in the distal portion of the TS,[4] it is reasonable to hypothesize that in some individuals large arachnoid granulations could produce relative luminal compromise and lead to a disturbed flow with a pressure gradient or an increased risk of venous thrombosis. Taken together, these data indicate that obstruction of the distal portion of one or both TS, which occurs in many patients with IIH,[2,3,5] is probably due to an intraluminal process (prominent arachnoidal granulations, thrombus forming on arachnoidal granulations, or venous thrombosis) rather than to an extrinsic cause (i.e., raised intracranial pressure), which should collapse the walls of the entire TS and not just the walls of the distal portion. Consistent with this hypothesis, a recent paper[5] described a patient with IIH who showed, on venography and manometry, a partial obstruction of the distal portion of both TS with raised pressure proximal to the obstruction. Dilatation of one of the transverse sinuses with a stent reduced both the pressure gradient and CSF opening pressure with striking symptomatic improvement, suggesting a causal relationship between venous outflow obstruction and IIH. Finally, we agree with King et al.[1] that raised intracranial pressure could make the obstruction worse by collapsing the walls of the sinus, thus further exacerbating both venous hypertension and CSF pressure.

A. Quattrone, MD, F. Bono, MD, K. Pardatscher, MD,
Catanzaro, Italy

To the Editor: King et al.[1] reported the results of cerebral venous sinus manometry and cervical puncture in IIH. They reported cerebral venous sinus hypertension in the superior sagittal and proximal TS that was reversed by reducing intracranial pressure. They concluded that the elevated intracranial pressure and not the other way around caused compression of the dural walls of the TS. Lee and Brazis[6] previously performed a prospective study to evaluate for the presence or absence of dural sinus thrombosis using MRI and MRV of the brain in 22 consecutive young, overweight women with typical IIH. None of the 22 MRI and MRV studies showed venous sinus thrombosis, and they concluded that MRV might not add significantly to the evaluation of typical IIH. I still order cranial MRI/MRV, however, in atypical IIH cases (e.g., male, thin, or elderly patients).

I have been impressed by the number of MRV studies in IIH that have shown findings that we have in the past interpreted as being suggestive of venous sinus stenosis or flow-related turbulence at the level of the distal transverse sinus. Some of these patients underwent standard catheter venography, and a few were even considered for possible stenting. Thus, the MRV studies in these patients actually confounded the evaluation of their IIH. My questions for the authors are as follows:

1. Did any of their patients undergo MRV in addition to cranial MRI, and if so did these MRV show anything that might have been misinterpreted as venous sinus thrombosis or obstruction at the distal TS?
2. Do the authors believe that performing an MRV in typical IIH might be misleading in the management of typical IIH in cases with flow-related abnormalities (but not true obstruction) at the distal TS?
3. Would pre- and postlumbar puncture MRV be able to demonstrate the reversibility of flow-related signal abnormalities at this level?

This work is fascinating, and I commend the authors for their efforts in this area.

Andrew G. Lee, MD, *Iowa City, IA*

To the Editor: We disagree with the conclusions of King et al.[1] and with the enthusiasm with which they were greeted in the accompanying editorial.[7] We also have found pressure gradients across stenoses in the lateral sinuses in patients with apparent IIH. Furthermore we have dilated one of these stenoses with a stent, thereby reducing the pressure gradient, which resulted in almost complete resolution of symptoms.[5] Hence, we strongly support the original King et al. hypothesis that venous outflow obstruction is the primary cause of IIH, at least in some cases.

There is no doubt that the TS may collapse in response to raised intracranial pressure and that in this situation pressure gradients

will be detected along them. Moreover, these gradients will resolve if intracranial pressure is reduced.[8] Equally, narrowing or occlusion of the intracranial venous sinuses can cause that raised intracranial pressure. With reference to this paper, it is important to reiterate that raised intracranial pressure in patients with unequivocal cerebral venous thrombosis is relieved by CSF diversion.[1] Where there is stenosis or thrombosis of the sagittal or transverse sinuses, a secondary rise in cerebral venous pressure must be accompanied by an even greater rise in CSF pressure if CSF absorption is to continue. Where cerebral venous pressure or intracranial pressure is raised, there will be an autoregulatory vasodilatation to maintain cerebral blood flow constant in the otherwise healthy brain. If CSF is diverted and intracranial pressure reduced, such cerebral vasodilatation will reverse, very likely with a fall in cerebral venous pressure.[9] A fall in cerebral venous pressure in response to a withdrawal of CSF, therefore, does not exclude venous outflow obstruction as the cause of raised intracranial pressure.

Another question, not explored, is any secondary effect of raised intracranial pressure on the venous sinuses when intracranial hypertension is due to venous sinus obstructions, especially at points where the sinuses are known to be compressible. In the cranial cavity the raised intracranial pressure itself will act as a force on the sinus wall, resisting any expansion that might mitigate the obstructing lesion. Reducing intracranial pressure by removing CSF would alter this transmural gradient and might allow the sinus to expand. If this expansion were sufficient, then the intrasinus pressure gradients across the stenotic lesions would fall acutely, in the manner recorded by King et al.[1] One can speculate further that after this acute response equilibrium will be restored at a rate depending on the degree of "primary" sinus stenosis and the compliance of the sinus wall under strain from rising intracranial pressure—paralleling the clinical effects of CSF withdrawal.

Whatever the mechanism operating here, we suggest that if pressure gradients along the TS were always secondary to IIH, then dilating one of these stenotic areas would not have caused the intracranial pressure to fall nor effected the clinical improvement we observed in our reported case. We applaud the pioneering observations of King et al. from 1995[10] but are anxious that a misinterpretation of their most recent results, unquestioned in your editorial, will stall a line of research that may yet revolutionize our understanding of this condition.

J. Nicholas, P. Higgins, John D. Pickard, *Cambridge, UK*

Reply from the Authors: We thank Dr. Quattrone et al. for their comments about our article on manometry combined with cervical puncture in IIH.[1] Our patients all had IIH, which is different from isolated intracranial hypertension without papilledema. There remains, however, a valid question as to the cause of the functional obstruction to cerebral venous outflow at the level of the TS. In our first paper, we considered mural thrombus, in some cases forming on arachnoidal granulations, the likely cause.[10] However, in IIH, where cerebral venography typically shows smooth bilateral tapered narrowing rather than focal sessile lesions, we now think that the changes are all due to stretching of the walls of the TS, given the immediate relief of elevated venous sinus pressures by lowering intracranial pressure with cervical puncture.

The case report of successful stenting of one TS in a patient with IIH[5] confirmed our findings of a pressure drop across the TS with raised pressures at the level of the torcula. The stent in the TS abolished the venous hypertension, and after 3 weeks the opening pressure at lumbar puncture was normal. The stent opened the lumen of the TS, dropped the pressure in the superior sagittal sinus, and allowed passive absorption of CSF, thereby lowering the intracranial pressure. Lowering the intracranial pressure by C1–2 puncture has the same effect, which leads us to consider that the TS stenosis is caused by extrinsic pressure on the walls of the TS rather than by intraluminal processes, such as mural thrombus. This argument begs the question as to what flattens the walls of the TS. We believe there is some process in IIH involving the arachnoidal granulations that impairs CSF absorption and initiates the rise in intracranial pressure.

MRV is recognized to be sensitive to altered flow but less accurate in assessing the anatomy of the venous sinuses. We consider conventional venography to be superior to MRV in displaying anatomic detail, and at this stage the smooth bilateral narrowing of the TS in IIH is unlikely to be due to mural thrombus.

Dr. Lee has drawn attention to the uncertain place of MRV in IIH. In typical cases of IIH we found the MRV lacked adequate definition in the TS, and flow voids could easily be misinterpreted as sinus thrombosis. MRV and conventional cerebral venograms were performed in patients with IIH, and most patients showed apparent narrowing of the TS on MRV; however, T2- and T1-weighted MRI excluded thromboses and arachnoidal granulations. We did not perform pre- and postcervical puncture MRV but would be surprised if this technique would be helpful because conventional venography did not show striking changes despite lowering of pressures in the superior sagittal sinus and proximal TS after cervical puncture.

Dr. Higgins and Professor Pickard question our conclusion that the venous outflow obstruction in IIH is due to partial collapse of the walls of the TS from raised intracranial pressure as a secondary phenomenon. By lowering intracranial pressure we found the pressure gradient in the TS largely disappeared. It is reasonable to assume that the cross-sectional area of the TS increased when the extrinsic compression was reduced. This would have the same effect as enlarging the internal dimensions by placement of a stent.

Conventional venograms in most instances of IIH show smooth, tapered narrowing of the TS bilaterally. Although we originally felt this could be due to mural thrombus, it seems unlikely that such a symmetrical appearance could result from acute, organized, or recanalized clot. If the process were some form of sclerosis of the TS, one would not expect lowering the intracranial pressure to have any significant effect on the venous hypertension.

Our hypothesis requires a subclinical elevation of intracranial pressure, possibly due to some change in permeability of arachnoidal villi to CSF. This could be produced by an as yet unidentified hormone in overweight females or by drugs such as minocycline. Over a period of a few months, in susceptible individuals the raised intracranial pressure would start to flatten the walls of the TS and push up the venous pressure in the superior sagittal sinus and proximal TS, further impairing CSF absorption and sharply elevating intracranial pressure. Stenting one TS would allow venous pressure to fall, but would the intracranial pressure fall to normal, as happened in the case reported by Higgins et al?[5] The early value of stenting the TS in IIH has been confirmed in a further four cases,[11] and the procedure offers a new treatment option. The follow-up results are awaited; however, these cases suggest that cerebral venography and manometry should be done routinely in IIH.

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Economy class stroke syndrome

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Neurology 2002;59;962-964
DOI 10.1212/WNL.59.6.962-b