



Iodine-123-Iomazenil SPECT Revealed Recovery of Neuronal Viability in Association with Improvement in Symptoms Following Treatment for Obstructive Hydrocephalus due to a Giant Posterior Cerebral Artery Aneurysm

Ryo Horiuchi, Hideyuki Yoshioka, Kazuya Kanemaru, Koji Hashimoto, Takashi Yagi, Hiroaki Murayama, Hiroyuki Kinouchi

Key words

- Giant aneurysm
- Hydrocephalus
- Iomazenil
- Neuronal recovery
- SPECT

Abbreviations and Acronyms

CBF: Cerebral blood flow
CBZ: Central benzodiazepine
¹²³I-IMZ: ¹²³I-iomazenil
MR: Magnetic resonance
PCA: Posterior cerebral artery
PET: Positron emission tomography
SPECT: Single-photon emission computed tomography

Department of Neurosurgery, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Yamanashi, Japan

To whom correspondence should be addressed:
 Hiroyuki Kinouchi, M.D., Ph.D.
 [E-mail: hkinouchi@yamanashi.ac.jp]

Citation: *World Neurosurg.* (2020) 137:341-344.
<https://doi.org/10.1016/j.wneu.2020.02.067>

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

1878-8750/\$ - see front matter © 2020 Elsevier Inc. All rights reserved.

INTRODUCTION

The radioligand ¹²³I-iomazenil (¹²³I-IMZ) binds to central benzodiazepine (CBZ) receptors, which are expressed strongly in the membrane of neurons,¹ and single-photon emission computed tomography (SPECT) using this ligand has been used in clinical practice mainly for epilepsy on the basis that the density of CBZ receptors is decreased in the epileptogenic tissue of patients with partial epilepsy.² ¹²³I-IMZ SPECT study is usually conducted in 2 phases: images obtained within 30 minutes after administration of ¹²³I-IMZ (early images) are well correlated with cerebral blood flow (CBF),³ and those obtained at 180 minutes after tracer injection (late images) reflect

■ **BACKGROUND:** Early and late images of ¹²³I-iomazenil (¹²³I-IMZ) single-photon emission computed tomography (SPECT) are considered to show cerebral blood flow and neuronal activity, respectively, and this modality may demonstrate temporal dysfunction of the frontal lobes in obstructive hydrocephalus. In this report, we examined ¹²³I-IMZ SPECT in a patient with chronic obstructive hydrocephalus owing to compression of the aqueduct by a partially thrombosed aneurysm of the left posterior cerebral artery for the first time.

■ **CASE DESCRIPTION:** A woman aged 77 years presented with progression of cognitive decline, gait disturbance, and urinary incontinence. She had a medical history of epilepsy and subarachnoid hemorrhage due to a ruptured left posterior cerebral artery aneurysm, treated conservatively when she was age 56 years. Magnetic resonance imaging revealed a mass lesion in the pineal region, which showed a target sign with gadolinium-based contrast agents, causing obstructive hydrocephalus owing to compression of the cerebral aqueduct. A right vertebral angiogram confirmed the presence of a partially thrombosed giant aneurysm at the left posterior cerebral artery. To rule out the involvement of nonconvulsive status epilepticus in her pathology, we performed ¹²³I-IMZ SPECT, and both early and late images demonstrated low uptake in the bilateral frontal cortex. After surgical trapping of the parent artery and resection of the aneurysm, hydrocephalus was relieved, and the symptoms disappeared along with improvement in early and late ¹²³I-IMZ SPECT images.

■ **CONCLUSIONS:** The findings in the present case indicate that ¹²³I-IMZ SPECT can detect reversible cerebral blood flow reduction and neuronal viability in the frontal lobes, which may affect the clinical manifestation of obstructive hydrocephalus.

neuronal activity.⁴ Further, recent reports have suggested that late images may demonstrate reversible neuronal damage or dysfunction, which cannot be demonstrated with conventional imaging modalities, such as computed tomography or magnetic resonance (MR) imaging, because the binding affinity of CBZ receptors was reversibly attenuated during the acute stage of brain injury, and recovers during the chronic stage when cerebral metabolism normalizes.^{5,6} Thus early and late ¹²³I-IMZ SPECT images show CBF and cortical neuronal viability, respectively.

Obstructive hydrocephalus may present with headache and disturbance of consciousness owing to increased intracranial pressure when the onset is acute. However, when developed chronically, it manifests neurologic symptoms such as cognitive decline, gait disturbance, and urinary incontinence. Although the exact mechanisms of these clinical manifestations of the chronic onset type remain obscure, attenuated frontal lobe activity caused by constant pressure due to ventricular dilatation has been considered as the main locus of the symptoms,⁷⁻¹⁰ which would reduce CBF in the same region as the evidence of the

reduced activity.¹¹⁻¹⁴ Therefore ¹²³I-IMZ SPECT is expected to clarify the pathology of chronic hydrocephalus by demonstrating CBF and neuronal activity on early and late images, respectively.

In this report, we examined ¹²³I-IMZ SPECT in a patient with chronic obstructive hydrocephalus owing to a giant posterior cerebral artery (PCA) aneurysm, and detected reversible reduction of CBF and neuronal dysfunction in the frontal regions for the first time to our knowledge.

CASE DESCRIPTION

A woman aged 77 years was referred to our institution with gradual progression of cognitive decline, gait disturbance, and urinary incontinence over the last 6 months. She had a past medical history of epilepsy and subarachnoid hemorrhage due to a ruptured left PCA aneurysm, which was treated conservatively at a local clinic when she was age 56 years. On admission, cognitive decline was severe, and intellectual assessment using the revised version of the Hasegawa dementia scale and Mini-Mental State Examination was impossible because of the patient's poor response. Restriction in upward gaze, gait disturbance, and urinary incontinence were also observed.

MR imaging revealed a well-defined mass lesion in the pineal region, which showed a target sign with gadolinium-based contrast agents. The mass, which was 30 mm in the major axis, caused obstructive hydrocephalus owing to

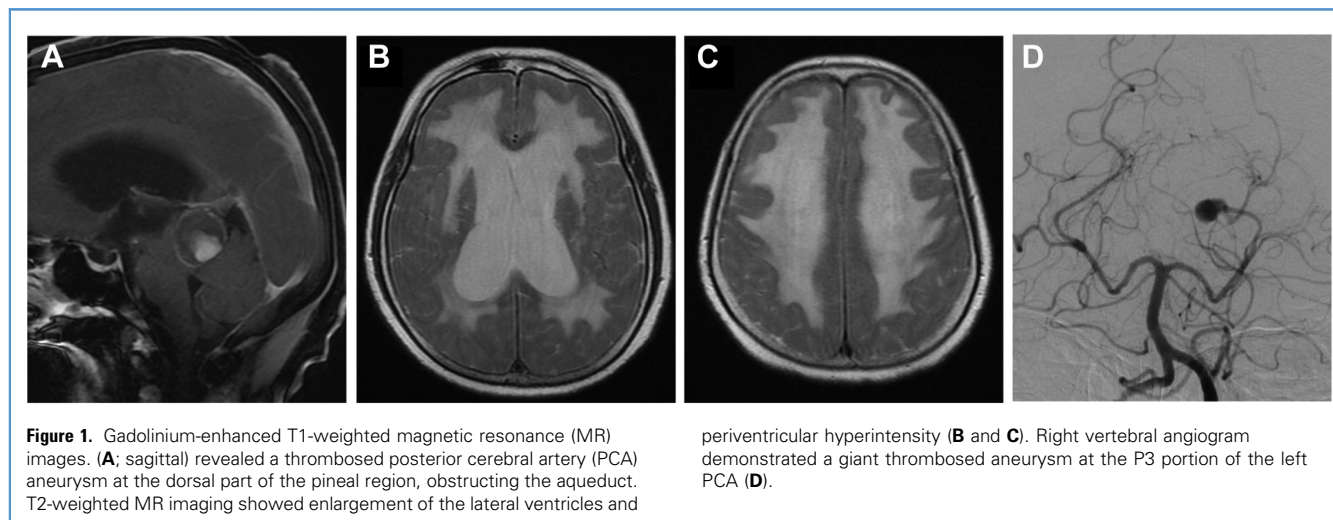
compression of the cerebral aqueduct (Figure 1A–C). A right vertebral angiogram confirmed the presence of a partially thrombosed giant aneurysm at the P3 portion of the left PCA (Figure 1D). No neurologic symptoms appeared during balloon test occlusion of the left PCA, suggesting tolerance to the parent artery occlusion. According to these results, she was diagnosed with obstructive hydrocephalus because of the partially thrombosed giant aneurysm of the left distal PCA. The institutional ethics committee at our institution reviewed and approved the protocol of the SPECT studies, and the patient's family provided written informed consent prior to participation. The second author of this article has obtained patient consent for anonymized publication of the case. To rule out the involvement of nonconvulsive status epilepticus in her pathology, we performed ¹²³I-IMZ SPECT, and both early and late images demonstrated remarkably low uptake of ¹²³I-IMZ in the bilateral frontal cortex (Figure 2A–D). She underwent trapping of the PCA and resection of the thrombosed giant aneurysm via a left occipital transtentorial approach. Her postoperative course was uneventful. Her cognitive impairment improved gradually, and intellectual assessment scores 3 months after surgery showed normal values (Hasegawa dementia scale 27, Mini-Mental State Examination 30). Improvement in gait disturbance and urinary incontinence was achieved as well. MR imaging 3 months

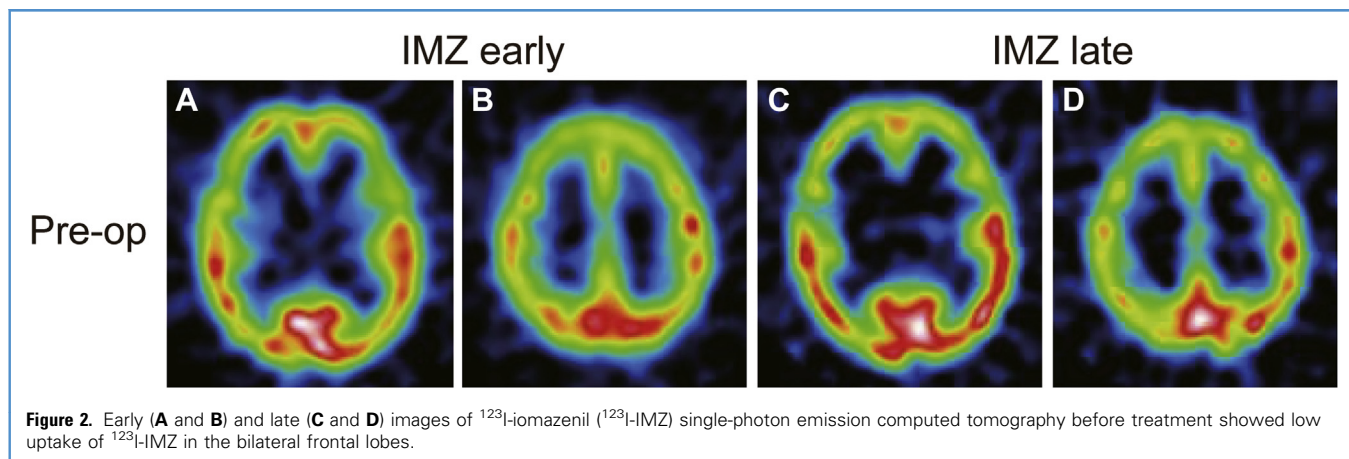
after surgery revealed relief of aqueductal compression on T1-weighted imaging (Figure 3A), and a significant reduction in the ventricle size and improvement in periventricular hyperintensity on T2-weighted imaging (Figure 3B and C). Postoperative CT angiography confirmed disappearance of the aneurysm (Figure 3D). Both early and late ¹²³I-IMZ SPECT images showed significant recovery of ¹²³I-IMZ uptake in the bilateral frontal lobes (Figure 4A–D).

DISCUSSION

In the present case report, early and late images of ¹²³I-IMZ SPECT detected the temporary attenuation of CBF and neuronal activity of the frontal lobes due to chronic obstructive hydrocephalus, and also revealed improvements in these findings after treatment for the first time.

Early images of ¹²³I-IMZ SPECT are well correlated with CBF images of ¹⁵O-positron emission tomography (PET).³ Thus the low uptake on the early image in the present case represents CBF reduction in the frontal lobes. A similar result was reported in a case with aqueductal stenosis in which CBF was significantly decreased in the frontal, parietal, and temporal lobes, and restored following surgery, as revealed by ^{99m}Tc-ethyl cysteinate dimer SPECT.¹¹ Also in patients with normal pressure hydrocephalus after subarachnoid hemorrhage, decreased CBF was detected by ¹⁵O-PET, especially in the lower frontal regions.¹² Another report of





patients with posterior fossa tumors causing hydrocephalus revealed reduction in the average hemispheric CBF with a ^{133}Xe inhalation method.¹³ Recently, the usefulness of arterial spin-labeled perfusion MR imaging in detecting reduction of CBF and its restoration after the alleviation of obstruction was reported in pediatric obstructive hydrocephalus patients, which would be an alternative noninvasive choice in assessing CBF.¹⁵ The exact mechanism of the reduction in regional CBF in chronic obstructive hydrocephalus is still unknown, but it should reflect a result of attenuated neuronal activity.¹⁴

Previous studies have demonstrated that late ^{123}I -IMZ SPECT images reflect neuronal activity. Therefore a reduction in uptake on this image indicates irreversible neuronal loss or transient neuronal dysfunction, which cannot be detected by ordinary

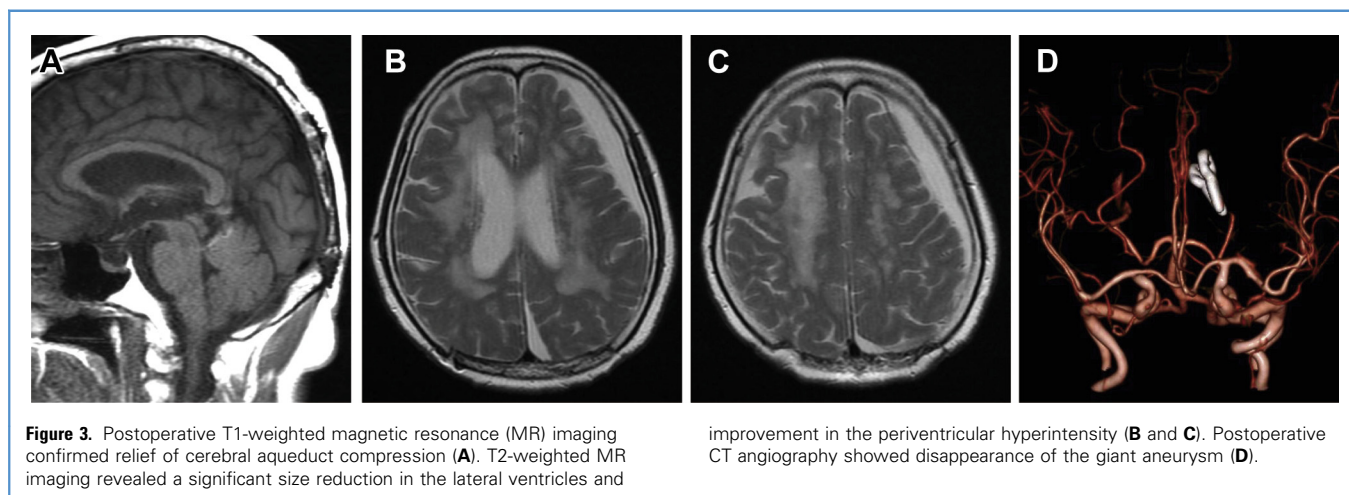
radiologic images, such as computed tomography or MR imaging, in various pathological conditions, such as epilepsy, stroke, and traumatic brain injuries.^{2,16-21} Recently, it has been shown that the reduced uptake in the cortex after head trauma is restored in the chronic phase as neurologic function improves.⁵ In addition, a reduction of uptake in the parenchyma surrounding a tumor was restored after surgical removal, and cognitive function improved.⁶ These findings suggest that neurocognitive function is correlated with ^{123}I -IMZ binding activity, and that ^{123}I -IMZ SPECT late images may have the potential to detect the viability of neurons. Consistent with these previous reports, we clearly demonstrated a reduction in ^{123}I -IMZ uptake on late images that was restored after surgical treatment for obstructive hydrocephalus; we also observed

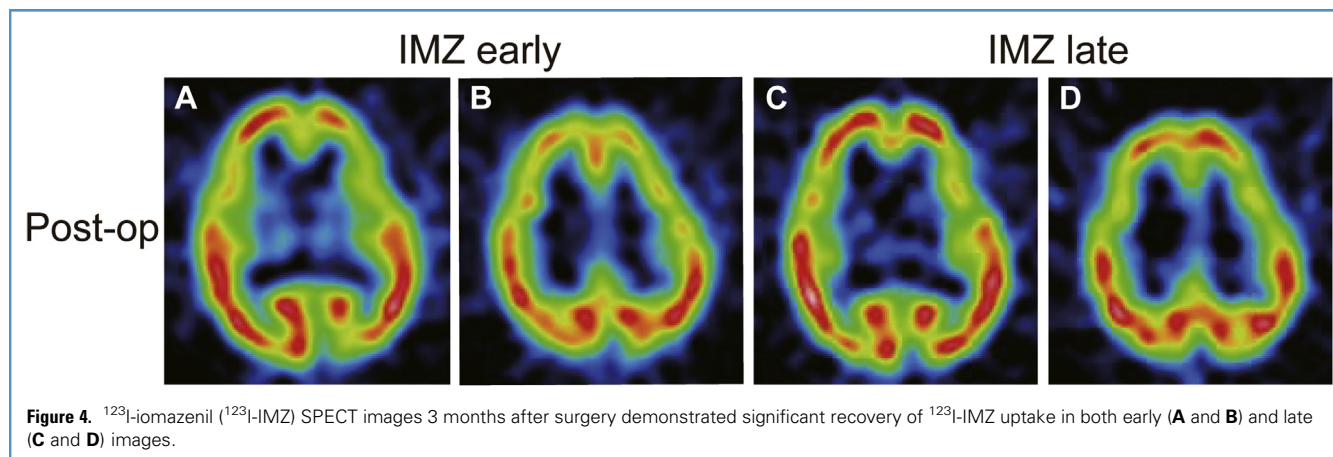
improvement in clinical symptoms in the present case.

The reduction in cerebral metabolism is thought to decrease the CBZ receptor binding affinity, leading to a reduction in ^{123}I -IMZ uptake on late images.²² ^{18}F -fluorodeoxyglucose PET showed a decrease in the cerebral metabolic rate of glucose in the left frontal lobe of a patient with chronic obstructive hydrocephalus, and it improved after the third ventriculostomy.⁹ Taken together, decreased uptake of ^{123}I -IMZ on late images can represent a reduction in cerebral metabolism that is because of the pathophysiology of chronic obstructive hydrocephalus.

CONCLUSIONS

We detected reversible reduction in CBF and neuronal viability in the frontal





regions in a patient with chronic obstructive hydrocephalus using ^{123}I -IMZ SPECT. Although further investigation with a large number of patients is necessary, this imaging modality may be beneficial for understanding the pathophysiological condition of hydrocephalus.

REFERENCES

- Beer HF, Bläuenstein PA, Hasler PH, et al. In vitro and in vivo evaluation of iodine-123-Ro 16-0154: a new imaging agent for SPECT investigations of benzodiazepine receptors. *J Nucl Med.* 1990;31:1007-1014.
- Umeoka S, Matsuda K, Baba K, et al. Usefulness of ^{123}I -iomazenil single-photon emission computed tomography in discriminating between mesial and lateral temporal lobe epilepsy in patients in whom magnetic resonance imaging demonstrates normal findings. *J Neurosurg.* 2007;107:352-363.
- Suzuki T, Ogasawara K, Kuroda H, et al. Comparison of early and late images on ^{123}I -iomazenil SPECT with cerebral blood flow and oxygen extraction fraction images on PET in the cerebral cortex of patients with chronic unilateral major cerebral artery occlusive disease. *Nucl Med Commun.* 2012;33:171-178.
- Onishi Y, Yonekura Y, Tanaka F, et al. Delayed image of iodine-123 iomazenil as a relative map of benzodiazepine receptor binding: the optimal scan time. *Eur J Nucl Med.* 1996;23:1491-1497.
- Koizumi H, Fujisawa H, Kurokawa T, et al. Recovered neuronal viability revealed by Iodine-123-iomazenil SPECT following traumatic brain injury. *J Cereb Blood Flow Metab.* 2010;30:1673-1681.
- Koizumi H, Ideguchi M, Iwanaga H, et al. Cognitive dysfunction might be improved in association with recovered neuronal viability after intracranial meningioma resection. *Brain Res.* 2014;1574:50-59.
- Mabe H, Suzuki K, Nagai H. Cerebral blood flow after ventriculoperitoneal shunt in children with hydrocephalus. *Childs Nerv Syst.* 1990;6:388-391.
- Nakada J, Oka N, Nagahori T, Endo S, Takaku A. Changes in the cerebral vascular bed in experimental hydrocephalus: an angio-architectural and histological study. *Acta Neurochir.* 1992;114:43-50.
- Wong CY, Luciano MG, MacIntyre WJ, Brunken RC, Hahn JF, Go RT. Viable neurons with luxury perfusion in hydrocephalus. *J Nucl Med.* 1997;38:1467-1470.
- Wozniak M, McLone DG, Raimondi AJ. Micro- and macrovascular changes as the direct cause of parenchymal destruction in congenital murine hydrocephalus. *J Neurosurg.* 1975;43:535-545.
- Garg AK, Suri A, Sharma BS, Shamim SA, Bal CS. Changes in cerebral perfusion hormone profile and cerebrospinal fluid flow across the third ventriculostomy after endoscopic third ventriculostomy in patients with aqueductal stenosis: a prospective study. *Clinical article. J Neurosurg Pediatr.* 2009;3:29-36.
- Ishikawa M, Kikuchi H, Taki W, et al. Regional cerebral blood flow and oxygen metabolism in normal pressure hydrocephalus after subarachnoid hemorrhage. *Neurol Med Chir (Tokyo).* 1989;29:382-388.
- Matsuda M, Takayama S, Matsumura K, Handa J. Postsurgical disappearance of dementia without increased cerebral blood flow in hydrocephalic patients. *Neurol Med Chir (Tokyo).* 1987;27:24-30.
- Phillips AA, Chan FH, Zheng MMZ, Krassioukov AV, Ainslie PN. Neurovascular coupling in humans: physiology, methodological advances and clinical implications. *J Cereb Blood Flow Metab.* 2016;36:647-664.
- Yeom KW, Lober RM, Alexander A, Cheshier SH, Edwards MSB. Hydrocephalus decreases arterial spin-labeled cerebral perfusion. *AJNR Am J Neuroradiol.* 2014;35:1433-1439.
- Chida K, Ogasawara K, Suga Y, et al. Post-operative cortical neural loss associated with cerebral hyperperfusion and cognitive impairment after carotid endarterectomy: ^{123}I -iomazenil SPECT study. *Stroke.* 2009;40:448-453.
- Hatazawa J, Satoh T, Shimosegawa E, et al. Evaluation of cerebral infarction with iodine ^{123}I -iomazenil SPECT. *J Nucl Med.* 1995;36:2154-2161.
- Hatazawa J, Shimosegawa E, Satoh T, Kanno I, Uemura K. Central benzodiazepine receptor distribution after subcortical hemorrhage evaluated by means of [^{123}I]iomazenil and SPECT. *Stroke.* 1995;26:2267-2271.
- Nakagawara J, Sperling B, Lassen NA. Incomplete brain infarction of reperfused cortex may be quantitated with iomazenil. *Stroke.* 1997;28:124-132.
- Ogasawara Y, Ogasawara K, Suzuki T, et al. Pre-operative ^{123}I -iomazenil SPECT imaging predicts cerebral hyperperfusion following endarterectomy for unilateral cervical internal carotid artery stenosis. *Am J Nucl Med Mol Imaging.* 2012;2:77-87.
- Sasaki M, Ichiya Y, Kuwabara Y, Yoshida T, Fukumura T, Masuda K. Benzodiazepine receptors in chronic cerebrovascular disease: comparison with blood flow and metabolism. *J Nucl Med.* 1997;38:1693-1698.
- Shiga T, Ikoma K, Katoh C, et al. Loss of neuronal integrity: a cause of hypometabolism in patients with traumatic brain injury without MRI abnormality in the chronic stage. *Eur J Nucl Med Mol Imaging.* 2006;33:817-822.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 19 December 2019; accepted 10 February 2020

Citation: *World Neurosurg.* (2020) 137:341-344.

<https://doi.org/10.1016/j.wneu.2020.02.067>

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

1878-8750/\$ - see front matter © 2020 Elsevier Inc. All rights reserved.