Editors' Note: In "Clinical Reasoning: A young woman with respiratory failure, hearing loss, and paraplegia," Ntranos et al. discussed the case of a patient with lesions in the globus pallidi, spinal cord, and cochleae in the setting of opioid overdose and respiratory failure. They concluded that the patient's neurologic syndrome was related to hypoxia. Commenting on this article, Dr. Berg asks the authors whether they considered the possibility of methylmalonic acidemia (MMA) as a potential underlying susceptibility factor because the lesions on the patient's MRI in the globus pallidi are characteristic of MMA. He suggests testing the patient's urine for MMA and blood for B12 level. Dr. Ntranos confirms that they checked the methylmalonic acid serum level, which was undetectable. Commenting on the same article, Drs. Bhatt and Adams propose that the patient's cochlear injury is related directly to opiate toxicity rather than hypoxia. Ntranos et al. stand by their hypothesis, explaining that the patient referenced by Bhatt and Adams was using multiple toxic substances for which the composition is unknown and that the presence of opiate receptors in cochlear cells does not mean that their stimulation will cause neurotoxicity. They suggest that additional research is needed to determine the direct effect of opiate use in cochlear cells.

—Chafic Karam, MD, and Robert C. Griggs, MD

until the stress of the opioid overdose or an acquired form due to severe B12 deficiency. If the authors did not check, it may be worthwhile to perform a follow-up test on the patient's urine sample for MMA and blood for B12 level. Even if results are normal, I wonder whether the patient has an underlying energy metabolism disorder that clinically manifested with the acute stressor given the particular combination of the lesions.

1. Ntranos A, Shoirah H, Dhamoon MS, et al. Clinical Reasoning: a young woman with respiratory failure, hearing loss, and paraplegia. *Neurology* 2017;88:e78–e84.

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AUTHOR RESPONSE: CLINICAL REASONING: A YOUNG WOMAN WITH RESPIRATORY FAILURE, HEARING LOSS, AND PARAPLEGIA

Achilles Ntranos, New York: I thank Dr. Berg for the thoughtful comments on our article.¹ Methylmalonic acidemia is indeed an important consideration for this case. We included a methylmalonic acid serum level in our initial workup, which was undetectable.

1. Ntranos A, Shoirah H, Dhamoon MS, et al. Clinical Reasoning: a young woman with respiratory failure, hearing loss, and paraplegia. *Neurology* 2017;88:e78–e84.

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LETTER RE: CLINICAL REASONING: A YOUNG WOMAN WITH RESPIRATORY FAILURE, HEARING LOSS, AND PARAPLEGIA

Michel J. Berg, Rochester, NY: I read with interest the case presented by Ntranos et al.¹ of acute-onset bilateral lesions in the globus pallidi, hearing loss (possible cochlear dysfunction), and upper thoracic anterior spinal cord lesion in a patient with an opioid/acetaminophen overdose and possible transient hypoxia. Did the authors consider the possibility of methylmalonic acidemia (MMA) as a potential underlying susceptibility factor? The lesions on the patient's MRI in the globus pallidi are characteristic of MMA. There are several possibilities, including an unrecognized minor mutation in the MMA pathway resulting in partial loss of function that was subclinical

LETTER RE: CLINICAL REASONING: A YOUNG WOMAN WITH RESPIRATORY FAILURE, HEARING LOSS, AND PARAPLEGIA

Nirav Bhatt, David Adams, Miami, FL: Ntranos et al.¹ presented a case of a 35-year-old woman with acute respiratory failure, hearing loss, and paraplegia. After discussing the differential diagnosis, they concluded that the likely cause of her symptoms was diffuse hypoxic injury of the involved structures.

While global hypoxia can cause bilateral basal ganglia infarctions and anterior spinal artery syndrome, it is a rather unlikely cause of bilateral cochlear injury. Contrariwise, there is substantial evidence to support

direct cochlear toxicity as a result of chronic opioid use and opioid overdose.² Animal studies have shown the presence of opioid receptors in the cochlea,³ and overstimulation of kappa receptors decreasing afferent activity from the cochlea may play a role in mediating this direct toxicity.

The patient described was confirmed to have an opioid overdose, and her bilateral hearing loss may be the result of direct cochlear injury as opposed to hypoxic injury, the latter mechanism being poorly supported in the literature. Thus, we propose 2 separate mechanisms from opioid overdose leading to the patient's constellation of symptoms: (1) direct cochlear toxicity leading to bilateral hearing loss and (2) hypoxemia leading to the anterior spinal artery syndrome and bilateral globus pallidus infarctions.

1. Ntranos A, Shoirah H, Dhamoon MS, et al. Clinical Reasoning: a young woman with respiratory failure, hearing loss, and paraplegia. *Neurology* 2017;88:e78–e84.
2. Schweitzer VG, Darrat I, Stach BA, Gray E. Sudden bilateral sensorineural hearing loss following polysubstance narcotic overdose. *J Am Acad Audiol* 2011;22:208–214.
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AUTHOR RESPONSE: CLINICAL REASONING: A YOUNG WOMAN WITH RESPIRATORY FAILURE, HEARING LOSS, AND PARAPLEGIA

Achilles Ntranos, Hazem Shoirah, Mandip S. Dhamoon, New York; David Hahn, Greenwich, CT; Thomas P. Naidich, Susan Shin, New York: We thank Drs. Bhatt and Adams for the thoughtful comment on our article.¹ Hypoxia affects cochlear function in many ways,^{2–5} including a rapid decline in both endocochlear and other cochlear potentials (i.e., cochlear microphonic, distortion-product otoacoustic emission, and compound action potential),^{6,7} as well as inducing histologic and cellular changes.⁸ Moreover, hypoxia, in the form of apneic spells, is a significant clinical predictor of newborn sensorineural hearing loss.⁹

A cytotoxic effect of opiate use is an important consideration and could potentially have contributed to the patient's hearing loss.¹ Although opiates can have a direct cytotoxic effect in cells, the causal relationship to hearing loss cannot be established because the patient

referenced by Bhatt and Adams was using multiple toxic substances (heroin, alcohol, crack cocaine, and benzodiazepines) for which the composition is unknown.¹⁰

The presence of opiate receptors in cochlear cells does not mean that their stimulation will cause neurotoxicity. A lack of correlation between opiate-induced toxicity and their ability to activate opiate receptors was previously identified.¹¹ Further research is needed to determine the direct effect of opiate use in cochlear cells.

The most likely mechanism of cochlear injury in the reported patient was the prolonged global hypoxic state induced by oxycodone overdose.¹

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CORRECTION

Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease

In the article “Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease” by D.S. Knopman et al.,¹ there are errors in table 2 for values entered under columns “Stage 2” and “Stage 3.” Please see the corrected table below.

REFERENCE

1. Knopman DS, Jack CR Jr, Wiste HJ, et al. Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease. *Neurology* 2012;78:1576–1582.

Table 2 Descriptive characteristics of participants by preclinical AD stage (with corrected values in boldface)

Characteristic	Stage defined by imaging and cognitive assessment ^a				
	Stage 0 (n = 127)	Stage 1 (n = 44)	Stage 2 (n = 39)	Stage 3 (n = 7)	SNAP group (n = 69)
Age, y, median (IQR)	77 (74, 80)	80 (75, 82)	80 (78, 82)	81 (80, 82)	81 (76, 84)
Female, n (%)	62 (49)	20 (45)	15 (38)	2 (29)	26 (38)
Education, y, median (IQR)	14 (12, 16)	14 (12, 16)	15 (12, 18)	14 (12, 16)	14 (12, 16)
APOE ε4 carrier, n (%)	31 (24)	15 (34)	16 (41)	5 (71)	8 (12)
MMSE score, median (IQR)	28 (28, 29)	28 (27, 29)	28 (27, 29)	27 (26, 28)	28 (27, 29)
No. of follow-up visits, n (%)					
One	96 (76)	38 (86)	33 (85)	7 (100)	56 (81)
Two	26 (20)	4 (9)	3 (8)	0 (0)	8 (12)
Three	3 (2)	2 (5)	3 (8)	0 (0)	3 (4)
Four	2 (2)	0 (0)	0 (0)	0 (0)	2 (3)
Years of follow-up, median (range)	1.3 (1.1, 5.1)	1.3 (1.2, 3.9)	1.3 (1.1, 4.1)	1.3 (1.2, 1.5)	1.3 (1.1, 5.1)
MCI/dementia diagnosis at 1 year, n (%)	6 (5)	5 (11)	8 (21)	3 (43)	7 (10)
Cognitive z scores, median (IQR) ^b					
Global	0.71 (0.18, 1.35)	0.47 (−0.00, 1.29)	0.34 (−0.27, 0.82)	−1.22 (−1.34, −1.00)	0.47 (−0.30, 1.11)
Memory	0.71 (0.13, 1.33)	0.75 (−0.16, 1.54)	0.40 (−0.31, 0.78)	−1.36 (−1.78, −1.13)	0.36 (−0.26, 1.22)
Language	0.49 (0.04, 1.09)	0.37 (−0.40, 0.90)	0.19 (−0.33, 0.80)	−0.90 (−1.02, −0.42)	0.27 (−0.38, 1.07)
Executive	0.66 (0.10, 1.09)	0.44 (−0.17, 1.13)	0.12 (−0.38, 0.92)	−0.64 (−0.92, −0.03)	0.03 (−0.48, 0.96)
Visuospatial	0.63 (0.03, 1.18)	0.62 (0.24, 1.39)	0.44 (−0.10, 0.85)	−1.43 (−1.60, −0.77)	0.35 (−0.49, 0.89)
PiB ratio, median (IQR)	1.33 (1.29, 1.38)	1.86 (1.64, 2.11)	1.93 (1.67, 2.29)	2.16 (1.90, 2.29)	1.34 (1.30, 1.39)
FDG ratio, median (IQR)	1.46 (1.39, 1.52)	1.43 (1.39, 1.53)	1.27 (1.21, 1.30)	1.23 (1.17, 1.30)	1.28 (1.25, 1.33)
Adjusted hippocampal volume, median (IQR)	0.39 (−0.19, 0.84)	0.36 (−0.09, 0.77)	−0.46 (−0.97, 0.10)	−0.87 (−1.07, −0.71)	−0.54 (−0.82, −0.14)

Abbreviations: AD = Alzheimer disease; CN = cognitively normal; FDG = fluorodeoxyglucose; IQR = interquartile range; MCI = mild cognitive impairment; MCSA = Mayo Clinic Study of Aging; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B.

^a Stage 0, all biomarkers normal; stage 1, abnormal PiB-PET; stage 2, abnormal PiB-PET and falling abnormal on at least one neurodegeneration biomarker; stage 3, abnormal PiB-PET, neurodegeneration and cognitive z score; SNAP, suspected non-Alzheimer pathway, where at least one neurodegeneration biomarker is abnormal with normal PiB-PET with or without abnormal cognition.

^b The median global cognitive z scores are >0 for the study group, which reflects their volunteer nature and the fact that about three-fourths of subjects had had one or more cognitive testing sessions before the PET baseline visit.

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