

[CASE REPORT]

Vertebral Artery Dissection after Exposure to Levofloxacin: A Report of Two Cases

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Abstract:

Exposure to quinolones is known to be an independent risk factor for aortic dissection; however, the association with vertebral artery dissection remains unclear. We report two cases of vertebral artery dissection that occurred 4 and 8 days after exposure to levofloxacin, respectively. Both patients had risk factors for vertebral artery dissection, and quinolone use could have been avoided. These two cases indicate that quinolone exposure can be a risk factor for vertebral artery dissection. Considering the possible mechanism, it is better to avoid the prescription of quinolones to patients who have insufficient connective tissues to avoid vertebral artery dissection.

Key words: vertebral artery dissection, quinolone, drug adverse effect

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Introduction

Exposure to quinolones is an independent risk factor for aortic dissection (1). In addition, a recent study has reported that the use of quinolones can also be a risk factor for carotid artery dissection (2). In the same study, vertebral artery dissection, a form of cervical artery dissection, was not reported to be associated with the use of quinolones (2). However, the relationship between the use of levofloxacin and vertebral artery dissection is unclear. This suggests that the study was underpowered to definitively prove the relationship between quinolone exposure and vertebral artery dissection. Therefore, physicians should be alert to the use of quinolones in patients who are at high risk of vertebral artery dissection. We herein report two cases of vertebral artery dissection at 4 and 8 days after exposure to quinolones, respectively.

Case Reports

Case 1

A 45-year-old man presented to the emergency depart-

ment with sudden-onset left posterior neck pain and left hemiparesis. His medical history included hypertension, dyslipidemia, and diabetes mellitus, and he had taken levofloxacin orally for a sore throat and cough for 8 days. He had no history of connective tissue disease or head and neck trauma. His vital signs were normal, except for high blood pressure (152/95 mmHg). A neurological examination revealed nystagmus, left hemifacial hypoalgesia, left-sided deficit of cranial nerves VII, IX, and X and paralysis of the left upper limb. Magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) of the brain revealed left vertebral artery dissection and infarction of the left medulla (Fig. 1, 2). A diagnosis of Wallenberg syndrome associated with vertebral artery dissection was made. He received conservative therapy and was subsequently transferred to a rehabilitation hospital on day 30. He had a Modified Rankin Scale score of 3.

Case 2

A 66-year-old man was transferred to the hospital for the treatment of pancreatitis with pancreatic abscess. His medical history included hypertension, diabetes mellitus, and chronic obstructive pulmonary disease. The patient developed duodenal stenosis caused by the pancreatic abscess and

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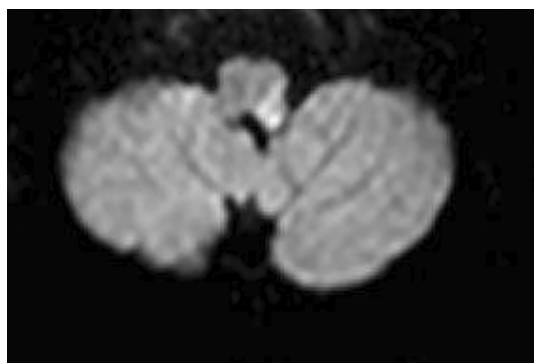


Figure 1. On diffusion-weighted magnetic resonance imaging, the left lateral medulla showed a high signal intensity.

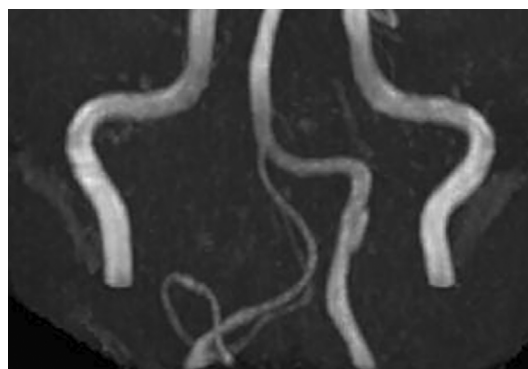


Figure 2. Magnetic resonance angiography showed dilation of the left vertebral artery with irregularity.



Figure 3. Magnetic resonance angiography showed dilation of the left vertebral artery with focal stenosis.

was treated with laparoscopic bypass surgery. On postoperative day 5, he developed pneumonia and was initially treated with tazobactam/piperacillin. His antibiotic treatment was switched to intravenous levofloxacin on postoperative day 9. He developed sudden-onset left occipital pain on postoperative day 13. MRI/MRA performed on postoperative day 17 revealed left vertebral artery dissection (Fig. 3). His vital signs were normal, with no neurologic abnormalities, and MRI showed no complications of ischemic stroke. The administration of levofloxacin was continued until postoperative day 30. The patient was discharged on postoperative day 35 with no neurological complications.

Discussion

We report two cases of vertebral artery dissection that developed soon after the use of levofloxacin. Although it is unclear whether there is a causal relationship between the use of levofloxacin and vertebral artery dissection, these two cases suggest that the use of levofloxacin may be associated with the risk of vertebral artery dissection and that caution should be exercised.

An association between large artery dissection and the use of quinolones has been reported (1, 2). In a previous study, the use of fluoroquinolone was associated with a two- to three-fold higher risk of aortic dissection, with the risk increasing 10 days after fluoroquinolone exposure (1). Recent

studies have reported data that support that it is not fluoroquinolone exposure, but other factors that are associated with aortic dissection in patients who receive fluoroquinolone to treat infections (3, 4), however, even those studies could not fully rule out a causal relationship between fluoroquinolones and aortic dissection in certain patients (3, 4).

There are several possible mechanisms through which quinolones may cause arterial dissection. Quinolones have properties, such as chelation of several metal ions (e.g., calcium, magnesium, and aluminum), which are essential for type 1 collagen synthesis (1), the decreased expression and activity of lysyl oxidase, and the increased expression and activity of matrix metalloproteinases (1, 5). Type 1 collagen is a major component of the vessel wall (6), and a decrease of type 1 collagen may lead to vessel wall vulnerability. The lysyl oxidases are extracellular copper enzymes that initiate the crosslinking of collagens and elastin. These crosslinks provide the tensile strength and elastic properties of vascular walls. Some reports indicated that decreased expression of lysyl oxidase can be associated with vulnerability of arteries (7), which can result in aortic dissection and aneurysm (8). Matrix metalloproteinases are a family of proteolytic enzymes that degrade several components of the extracellular matrix and which mediate vascular remodeling, which may cause vascular dissection. In fact, increase serum levels of matrix metalloproteinase-9 have been reported to be associated with vertebral artery dissection (9). Thus, through these mechanisms, quinolones seem to have the potential to cause arterial dissection.

In addition, carotid artery dissection was recently reported to occur more frequently in patients who were exposed to quinolones (2). To date, there is no clear evidence that the use of quinolones is a risk factor for dissection in the intracranial artery or vertebral artery (2, 10); however, these results cannot be validated due to the small sample sizes of the studies. Moreover, these results should be validated outside of Europe because although internal carotid artery dissection is more common in Europe than in Asia, vertebral artery dissection may be more common in Asia than in Europe (11). Therefore, it may be possible that the use of quinolones increases the risk of vertebral artery dissection,

as observed in our two cases.

Quinolone is an overused antimicrobial drug. The defined daily dose per 1,000 inhabitants in Japan was 2.379 in 2018 (12). If quinolones can cause vertebral artery dissection, efforts to revisit the appropriate use of quinolones may reduce the incidence of vertebral artery dissection. The FDA recommends that quinolones not be used by individuals who are at risk for aortic dissection or aortic aneurysm (13). Similarly, since vertebral artery dissection can cause serious ischemic stroke, physicians should reconsider the need for quinolones in patients who have additional risk factors for vertebral artery dissection.

The authors state that they have no Conflict of Interest (COI).

References

1. Lee CC, Lee MG, Hsieh R, et al. Oral fluoroquinolone and the risk of aortic dissection. *J Am Coll Cardiol* **72**: 1369-1378, 2018.
2. Del Zotto E, Pezzini A. Use of fluoroquinolones and the risk of spontaneous cervical artery dissection. *Eur J Neurol* **26**: 1028-1031, 2019.
3. Gopalakrishnan C, Bykov K, Fischer MA, Connolly JG, Gagne JJ, Fralick M. Association of fluoroquinolones with the risk of aortic aneurysm or aortic dissection. *JAMA Intern Med* **180**: 1596-1605, 2020.
4. Dong YH, Chang CH, Wang JL, Wu LC, Lin JW, Toh S. Association of infections and use of fluoroquinolones with the risk of aortic aneurysm or aortic dissection. *JAMA Intern Med* **180**: 1587-1595, 2020.
5. LeMaire SA, Zhang L, Luo W, et al. Effect of ciprofloxacin on susceptibility to aortic dissection and rupture in mice. *JAMA Surg* **153**: e181804, 2018.
6. Ponticos M, Partridge T, Black CM, Abraham DJ, Bou-Gharios G. Regulation of collagen type I in vascular smooth muscle cells by competition between Nkx2.5 and deltaEF1/ZEB1. *Mol Cell Biol* **24**: 6151-6161, 2004.
7. Mäki JM, Räsänen J, Tikkanen H, et al. Inactivation of the lysyl oxidase gene *Lox* leads to aortic aneurysms, cardiovascular dysfunction, and perinatal death in mice. *Circulation* **106**: 2503-2509, 2002.
8. Guo DC, Regalado ES, Gong L, et al. *LOX* mutations predispose to thoracic aortic aneurysms and dissections. *Circ Res* **118**: 928-934, 2016.
9. Chen CY, Chang FC, Lee IH, Chung CP. Involvement of matrix metalloproteinase 9 in vertebral arterial dissection with posterior circulation ischemic stroke. *J Am Heart Assoc* **9**: e016743, 2020.
10. Maumus-Robert S, Debette S, Bérard X, Mansiaux Y, Tubert-Bitter P, Pariente A. Risk of intracranial aneurysm and dissection and fluoroquinolone use: a case-time-control study. *Stroke* **51**: 994-997, 2020.
11. Debette S. Pathophysiology and risk factors of cervical artery dissection: what have we learnt from large hospital-based cohorts? *Curr Opin Neurol* **27**: 20-28, 2014.
12. Japan Antimicrobial Resistance Clinical Reference Center. National Antimicrobial Sales Volume Surveillance [Internet]. [cited 2020 Dec 12]. Available from: <http://amrccr.ncgm.go.jp/surveillanc/e/020/20181128172618.html> (in Japanese)
13. FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients [Internet]. [cited 2020 Dec 12]. Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics>

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