

CASE REPORT

Nickel-associated delayed multiple white matter lesions after stent-assisted coil embolization of intracranial unruptured aneurysm

Hun Soo Park,¹ Ichiro Nakagawa,¹ Shohei Yokoyama,¹ Daisuke Wajima,¹ Takeshi Wada,² Yasushi Motoyama,¹ Kimihiko Kichikawa,² Hiroyuki Nakase¹

¹Department of Neurosurgery, Nara Medical University, Kashihara, Nara, Japan

²Department of Radiology, Nara Medical University, Kashihara, Nara, Japan

Correspondence to

Dr Ichiro Nakagawa, Department of Neurosurgery, Nara Medical University, Kashihara, Nara 6348522, Japan; nakagawa@naramed-u.ac.jp

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ABSTRACT

Metal-induced encephalopathy after stent-assisted coil embolization is extremely rare. The present report describes two patients who presented with symptomatic intracranial parenchymal edematous lesions after stent-assisted coil embolization. A 64-year-old woman underwent stent-assisted coil embolization for a left internal carotid artery aneurysm; 21 days after the procedure she presented with right hand weakness and MRI revealed multifocal white matter lesions. Another woman aged 52 years underwent stent-assisted coil embolization for right vertebral artery aneurysm; 18 days after the procedure she presented with left-sided sensory disturbance and MRI demonstrated multiple white matter lesions. Treatment in both cases resulted in improvement of these lesions after steroid pulse therapy, and the patients had no associated morbidity 4 months after the procedures. Clinicians should monitor for neurologic symptoms and postoperative delayed radiologic parenchymal edematous changes associated with the metal allergic reaction after nitinol stent-assisted coil embolization.

BACKGROUND

Stent-assisted coil embolization has emerged as a widespread treatment strategy for wide-necked cerebral aneurysms. Intracranial stents are hypothesized to improve aneurysmal occlusion by serving as a scaffold to prevent coil protrusion, enhancing coil packing density, and promoting re-endothelialization. However, intracranial nitinol stents contain nickel, which is still a matter of controversy because concerns have been raised about biocompatibility associated with potential nickel release inducing an allergic reaction to nickel.

Furthermore, little is known about nickel-associated delayed encephalopathy after nitinol stent-assisted procedures. The present report describes two patients with intracranial aneurysms after stent-assisted coil embolization who presented with symptomatic intracranial parenchymal edematous lesions, which may have been associated with nickel allergy.

CASE PRESENTATION

Case 1

A 64-year-old woman was incidentally found to have an unruptured left internal carotid artery (ICA) aneurysm. She had no history of nickel, titanium, or platinum allergy. Digital subtraction angiography (DSA) showed a saccular aneurysm located on the medial wall of the C3 portion of the left ICA, about 5 mm in maximum diameter and about 4 mm in neck diameter (figure 1). Stent-assisted coil embolization was performed because of instability of the microcatheter during embolization. An Enterprise VRD 2 stent (4.0×23 mm; Codman, Raynham, Massachusetts, USA) was placed in the aneurysmal neck and platinum detachable coils were put into the aneurysm. Finally, DSA findings demonstrated complete occlusion of the aneurysm (figure 2). She was discharged without neurologic deficit; however, 21 days after the procedure she presented with right hand weakness which continued to worsen. MRI revealed multifocal white matter lesions in the left cerebral hemisphere. These lesions were non-homogeneous and relatively hyperintense on diffusion-weighted imaging (DWI) and hyperintense on an apparent diffusion coefficient (ADC) map (figure 3). Blood and cerebral spinal fluid laboratory examinations did not show evidence of infectious disease or a

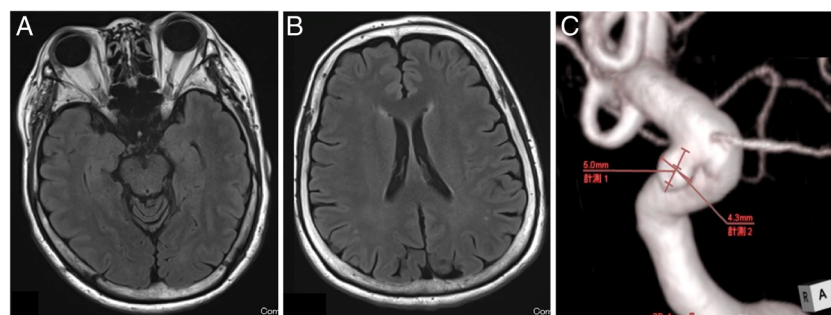


Figure 1 Case 1: (A, B) Preoperative MRI did not reveal the abnormal lesions. (C) Preoperative three-dimensional angiogram shows an internal carotid artery aneurysm located in the medial wall of the C3 portion.

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Neuroimaging

demyelinating disorder. The patient was treated with steroid pulse therapy consisting of methylprednisolone (1000 mg/day) for 3 days followed by oral prednisolone (20 mg/day), which was slowly tapered. A week after the medical treatment her right hand weakness fully improved. Three months after treatment, DSA demonstrated complete occlusion of the aneurysm and no findings of in-stent stenosis. Four months later, MRI demonstrated no ischemic or edematous lesions ([figure 3](#)).

Case 2

A 52-year-old woman with dizziness was introduced to our hospital. MR angiography showed a large right vertebral artery aneurysm. The aneurysm compressed the brainstem but



Figure 2 Case 1: (A, B) Postoperative digital subtraction angiogram shows complete occlusion of the aneurysm.

edematous change was not seen on MRI ([figure 4A](#)). DSA showed the aneurysm had a wide neck measuring 10.8 mm in diameter and a saccular aneurysm (13.9×8.6×12.7 mm) arising 4 mm distal to the posterior inferior cerebellar artery orifice to vertebralbasilar junction ([figure 4B, C](#)). Stent-assisted coil embolization was performed using an Enterprise VRD stent (4.0×23 mm), and platinum detachable coils were put into the aneurysm. The final DSA revealed total occlusion of the aneurysm ([figure 5](#)). Eighteen days after the procedure, however, she presented with abducens nerve palsy, right facial palsy, dysphagia, and left-sided sensory disturbance. MRI revealed multifocal fluid-attenuated inversion recovery high-intensity lesions in the right white matter regions, including the medulla, pons, thalamus, and corpus callosum. These lesions were isointense on DWI and hyperintense on the ADC map ([figure 6A–D](#)). She received medical treatment with steroid pulse therapy, as in case 1. Two months after the medical treatment her symptoms gradually improved, at which time follow-up MRI revealed improvement in the multifocal lesions which had disappeared 4 months after treatment ([figure 6E–G](#)). Skin patch testing for allergy including platinum, nickel, cobalt, and titanium before steroid pulse therapy showed a definite positive reaction to nickel ([figure 7](#)). Three months after the treatment, DSA demonstrated complete occlusion of the aneurysm without in-stent stenosis.

DISCUSSION

We present two patients with delayed symptomatic intracranial parenchymal edematous lesions after stent-assisted coil embolization for an unruptured aneurysm using a nitinol stent. We

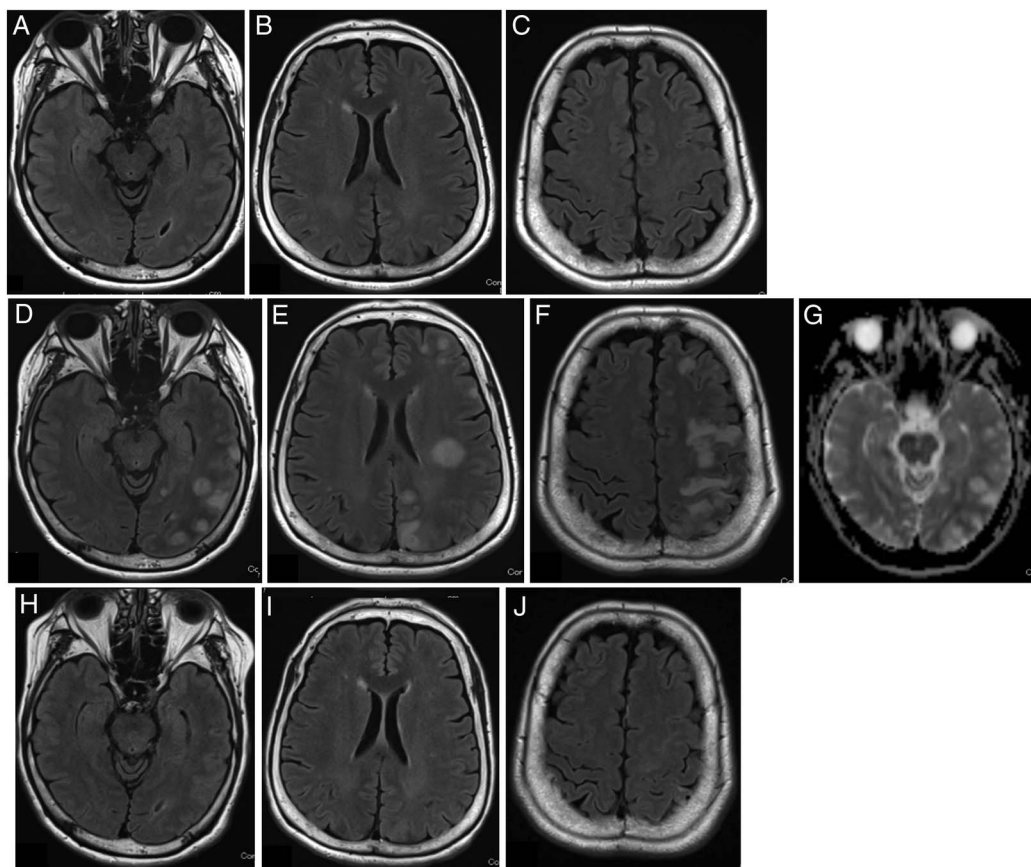


Figure 3 Case 1: (A–C) MRI shows no edematous changes 1 day after treatment. (D–F) Multiple hyperintensity lesions are seen 21 days later on follow-up MRI. (G) These lesions show high signals on apparent diffusion coefficient mapping. (H–J) Four months after treatment the edematous lesions have completely disappeared.

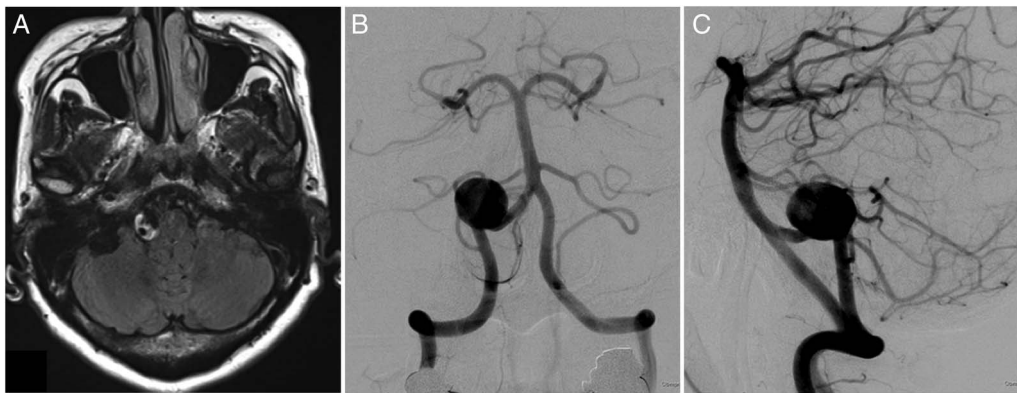


Figure 4 Case 2: (A) Preoperative MRI shows the aneurysm compressing the pons without edematous change. (B, C) Anteroposterior and lateral view digital subtraction angiograms show a right vertebral artery large aneurysm located 4 mm distal to the posterior inferior cerebellar artery orifice.

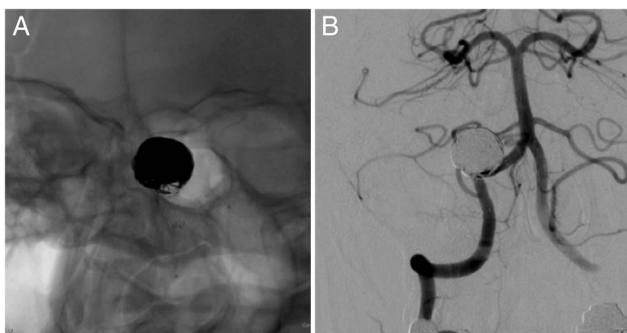


Figure 5 Case 2: (A, B) Postoperative digital subtraction angiogram shows complete occlusion of the aneurysm maintaining the parent artery.

presume that these reactions were the result of allergic hypersensitivity caused by the nickel component being released into the blood via the nitinol stent.

The use of intracranial stents has expanded significantly over the past decade, especially with the development of more flexible nitinol stents. Intracranial stents have been used for revascularization of atherosclerotic vessels, and their efficacy and safety have been reported.¹ More recently, the use of intracranial stents as a scaffold through which coils can be placed into the aneurysm has grown dramatically and has now become a commonly used technique in the treatment of large and wide-necked aneurysms. The Enterprise stent is a widely used self-expanding nitinol stent with a closed-cell design, specifically for the treatment of wide-necked intracranial aneurysms. While most coronary stents are constructed of 316L stainless steel which consists of approximately 12% nickel, many intracranial stents, including the Enterprise stent, consist of nitinol, an alloy that contains approximately 55% nickel and 45% titanium, which contributes to its flexibility and shape memory mechanics.

Nickel is a well-known allergen of concern to the medical industry because 7–15% of the general population and 16.2% of patients who present with contact dermatitis demonstrate hypersensitivity to nickel.^{2,3} It has been postulated that intracranial nitinol stents release nickel ions after exposure to direct blood circulation, and the serum nickel level increases slowly over time. A recent study showed that the mean serum nickel ion level after nitinol-containing intravascular device placement significantly increased at 24 hours, peaked at 1 month, and

declined to baseline at 12 months.⁴ They also showed that there are inter-individual differences in the timing of maximum serum levels of nickel after device placement, which indicates that multiple biological factors have an influence on nickel ion release from the stent. Serum nickel ions pose a risk of promoting an inflammatory response in the surrounding tissues by activating interleukin-1 β , intercellular adhesion molecules, and monocytes.⁵ These inflammatory mediators then induce intracranial parenchymal edematous lesions after stent-assisted coil embolization.

With regard to the duration of nickel ion release, the formation of a stable oxide film and a calcium phosphate layer on the stent after exposure to the bioenvironment suppresses any nickel contact in the body.⁶ Furthermore, endothelialization of the stent also plays an important role in the suppression of the release of nickel ions chronically. We found only one report where, following treatment of an intracranial aneurysm by nitinol stent-assisted coil embolization, reversible intracranial parenchymal change was observed 1 month after stent placement.⁷ In the two cases presented here the patients' symptoms began 3 weeks after stent-assisted coil embolization with a nitinol stent. These results are consistent with the peak level of serum nickel ions described in the previous report.⁴ Furthermore, skin patch testing before steroid pulse therapy revealed a definite positive reaction to nickel. Given the significant amount of nickel in intracranial nitinol stents, it is possible that inflammation derived from a hypersensitivity reaction to the nickel may cause delayed multiple white matter lesions. In contrast, previous reports have described cases of extensive cerebral edema after surgical clipping for the obliteration of a cerebral aneurysm. Patients developed pruritus and papular rash as well as headache and seizure with intracranial edema surrounding the nickel-containing aneurysm clip, which consisted of 14–16% nickel.^{8,9} These results suggest that intravascular devices like intracranial stents and also intracranial surgical devices applied outside a vessel such as nickel-containing aneurysm clips can induce parenchymal change as a result of a hypersensitivity reaction to the nickel.

Regarding the treatment of metal allergy, removal of the potentially offending implant is the most effective option. Removal of intravascular implants has been reported in the cardiovascular and peripheral vascular fields; however, removal of intracranial stents is impractical and carries a high risk. Administration of low-dose oral steroids is considered an initial option; however, little is known about the appropriate dose,

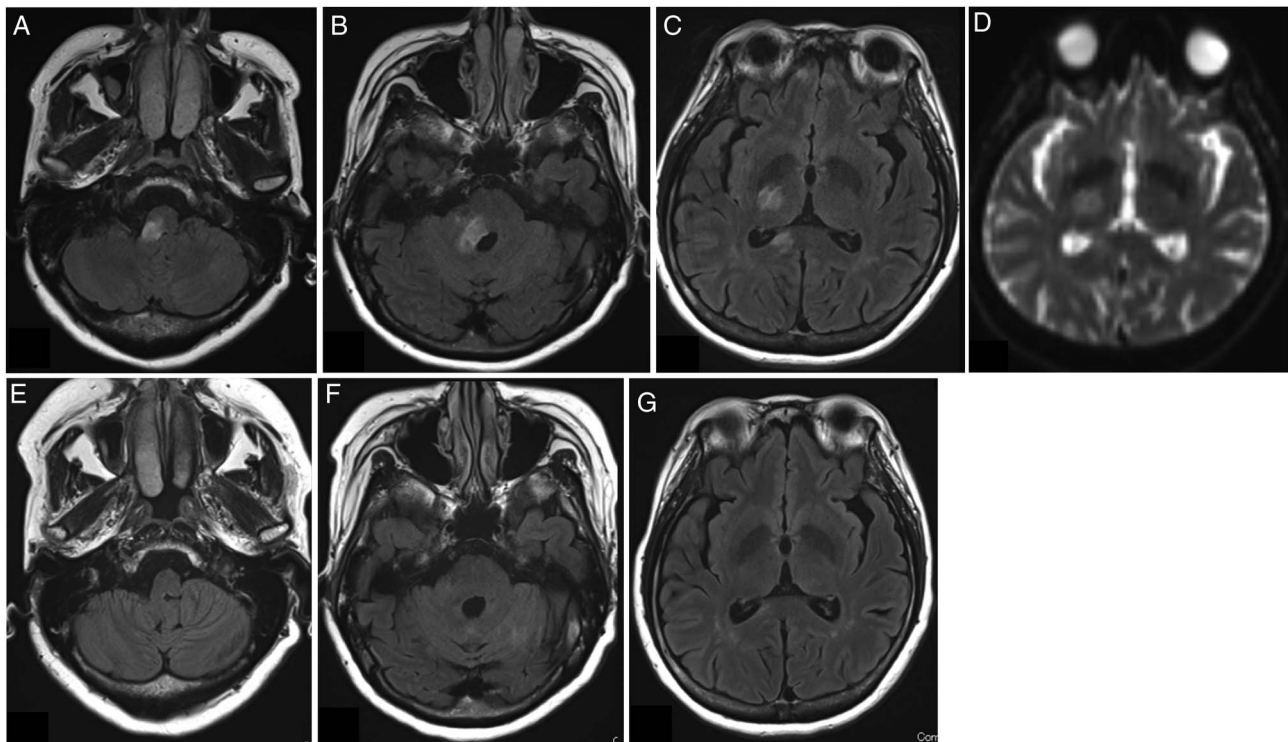


Figure 6 Case 2: (A–C) Multiple hyperintensity lesions appear 18 days later on follow-up MRI. (D) These lesions show high signals on apparent diffusion coefficient mapping. (E–G) Four months after treatment these edematous lesions are disappearing.

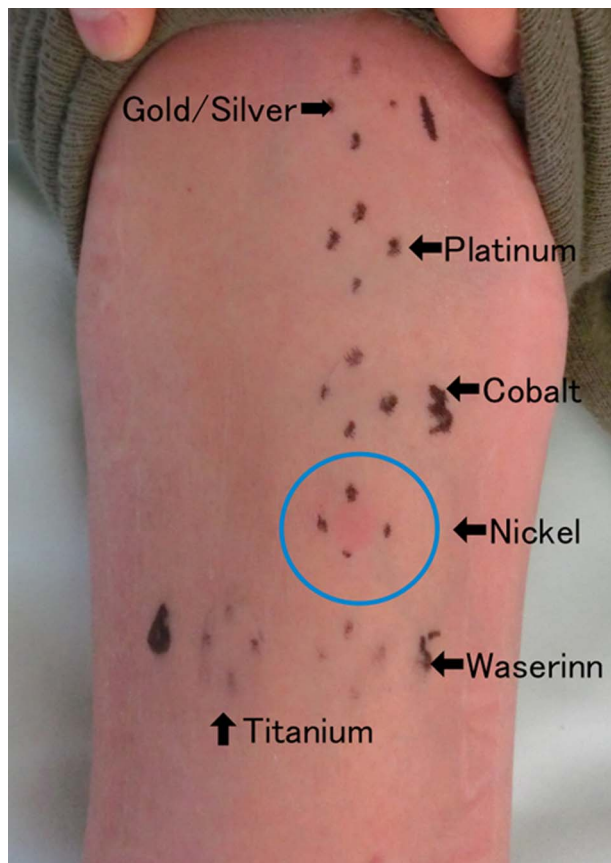


Figure 7 Case 2: Skin patch testing for allergy including platinum, nickel, cobalt, and titanium before steroid pulse therapy shows a definite positive reaction to nickel.

timing, and weaning of steroids for these lesions. The patients reported here were started on steroid pulse therapy for 3 days followed by oral prednisolone for 4 months because of progressive neurologic deficits, and both patients' symptoms improved and the edematous lesions completely disappeared.

Although the prevalence of contact allergy to metals is high, hypersensitivity complications associated with metal implants have been reported to be <0.1%.⁴ The preoperative interview may include assessment of a history of metal allergy and a patch test procedure may be useful for prediction of hypersensitivity; however, it is not possible to predict which patients may develop complications. Patch testing is notably unclear with regard to whether or not metal allergy directly causes the symptoms, and false-negative and false-positive results are frequent.^{2 3 10} Clinical surveillance will be necessary to determine whether skin patch testing will result in adequate identification of those at risk for the development of nickel hypersensitivity.

CONCLUSIONS

Allergic reaction to a nickel-containing stent may occur after stent-assisted coil embolization for the treatment of intracranial aneurysms. Clinicians should monitor for neurologic symptoms and postoperative delayed radiologic parenchymal edematous changes associated with metal allergic reaction after nitinol stent-assisted coil embolization.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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