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ABSTRACT

SUMMARY: Nickel is used in many cerebral endovascular treatment devices. However, nickel hypersensitivity is the most common metal allergy, and the relative risk of treatment in these patients is unknown. This retrospective analysis identified patients with nickel or metal allergies who underwent cerebral endovascular treatment with nickel-containing devices. Seven patients with nickel and/or other metal allergies underwent treatment with 9 nickel-containing devices. None experienced periprocedural complications. No patient received treatment with corticosteroids or antihistamines. At a mean clinical follow-up for all patients of 22.8 months (range, 10.5–38.0 months), no patients had symptoms attributable to nickel allergic reactions. The mean radiographic follow-up for all patients at 18.4 months (range, 2.5–37.5 months) showed successful treatment of the targeted vascular pathologies, with no evidence of in-stent stenosis or other allergic or hypersensitivity sequelae. The treatment of cerebrovascular lesions with a nickel-containing device resulted in no adverse outcomes among these patients and was safe and effective.

ABBREVIATION: DAPT = dual antiplatelet therapy

Nickel hypersensitivity is the most commonly documented metal allergy, with an estimated prevalence of 10% to 15% in the general population, predominantly affecting women.^{1,2} Nickel is used in the manufacturing of most new endovascular treatment devices for intracranial aneurysms, including nitinol-containing flow-diverting stents, self-expanding stents, and intrasaccular occlusion devices.^{3–7} Because these devices are increasingly used, the relative risk of adverse events when they are used in patients with nickel and other metal allergies should be more fully elucidated.

In the cardiac literature, particularly in retrospective studies, nickel allergy has been associated with an increased incidence of in-stent stenosis.^{8,9} However, prospective studies have not confirmed this relationship.^{10–12} Nevertheless, some concern remains regarding the questionable risk of using these devices in patients with documented metal allergies.¹³

In the cerebrovascular literature, a limited number of studies have addressed the use of nickel-containing devices in patients

with nickel allergies. Some reports have documented possible associated complications,^{3,4,6,14–16} while others have reported no serious adverse outcomes in this patient population.^{5,7}

In this study, we sought to review the perioperative management and outcomes of patients with documented nickel and other metal allergies who underwent endovascular cerebrovascular pathology treatment with nickel-containing devices.

Case Series

We performed a retrospective analysis using data from our prospectively collected endovascular database and identified patients with a documented nickel allergy or other metal allergy who underwent treatment with a permanently implanted nickel-containing device from July 2018 through March 2021. Institutional review board approval for the study was obtained. The requirement for informed consent for study participation was waived due to the retrospective nature of the study and the low risk to participants. All patients had given prior informed written consent for their treatment. From the database, we extracted demographic, clinical, and radiologic data, including angiographic results, medications, complications, and follow-up clinical and radiologic outcomes. All patient data were appropriately anonymized to maintain confidentiality.

Endovascular Procedures

Endovascular treatment procedures were performed with the patients placed under general anesthesia with neurophysiologic

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monitoring. Dermatologic testing was not performed to confirm the self-reported metal allergies of patients. The patients were not pretreated prophylactically with corticosteroids or antihistamines. Intraprocedural heparin was administered to all patients to maintain the goal of an activated clotting time 2–3 times that of baseline. All patients were receiving a dual antiplatelet therapy (DAPT) regimen at the time of device deployment, and this regimen was continued for at least 6 months after treatment.

Included Patients and Outcomes

Seven patients (mean age, 61.7 years; range, 40s–80s) with documented nickel allergies (4 patients) or other metal allergies (3 patients) who had 9 vascular lesions (7 saccular aneurysms, 1 blister or fusiform aneurysm, and 1 intracranial dissection) underwent treatment with a total of 9 nickel-containing devices (7 flow-diverting stents and 2 self-expanding intracranial stents) during 8 treatment sessions. All 7 patients were receiving a DAPT regimen at the time of treatment, with an adequate response verified on hematologic assays. DAPT was continued for at least 6 months in all 7 patients. No patient experienced any periprocedural complications, including any apparent allergic reactions, thromboembolic events, or in-stent stenoses. No patient received periprocedural prophylactic treatment with either corticosteroids or antihistamines for documented nickel or metal allergies.

Clinical, radiologic, and angiographic follow-up was performed at the interventionalist's discretion and in accordance with practice patterns. Clinical follow-up available for all 7 patients (mean, 22.8 months; range, 10.5–38.0 months) found no evidence of procedure-related neurologic symptoms or symptoms attributable to nickel or metal allergic reactions. Angiographic follow-up was available for 6 patients (mean, 5 months; range, 0.5–14.5 months). In 5 of these 6 patients, follow-up angiography demonstrated complete resolution of their 7 vascular lesions (complete obliteration of 6 saccular aneurysms and no dissection-associated flow aberration), with no evidence of in-stent stenosis, vasculitis-like changes, or other vessel pathology. In 1 of these 6 patients, short-interval follow-up angiography at 2 weeks demonstrated decreased aneurysm filling with marked contrast stagnation in a ruptured fusiform aneurysm after flow-diverting stent placement. Follow-up noninvasive imaging findings (MR imaging or MRA for 4 patients, CTA for 3 patients) were available for all 7 patients (mean, 18.4 months; range, 2.5–37.5 months).

None of these 7 patients showed any evidence of adverse outcomes attributable to nickel or metal allergy reactions, including increased small-vessel disease, WM lesions, vasculitis, or attributable ischemic changes (Online Supplemental Data).

DISCUSSION

Cases of cutaneous allergic reactions to metallic orthopedic and surgical implants are well documented.^{17,18} However, the evidence that endovascularly placed intravascular devices can induce a deleterious allergic response is more debatable. Although studies in the cardiology literature have associated nickel allergies with an increased incidence of in-stent stenosis,^{8,9,13} prospective studies have not confirmed this relationship.^{10–12} Nonetheless,

neuroendovascular surgeons and interventionalists may be wise to be concerned about placing nickel-containing devices in patients who have reported nickel or other metal allergies.¹⁹ Despite the overall prevalence of nickel allergies within the general population (10%–15%)^{1,2} and the increased use of nickel-containing devices for the treatment of cerebrovascular lesions, relatively few studies have been published on the subject.

Tonetti et al⁵ reported the successful treatment with a nickel-containing flow-diverting stent of 2 patients who had cutaneous nickel allergies; neither patient demonstrated any allergic reactions or in-stent stenosis at prolonged follow-up. As in our series of 7 patients, neither of their 2 patients had received periprocedural prophylactic treatment with steroids or antihistamines. Similarly, Wallace et al⁷ reported that, in a series of 20 patients with metal allergies who underwent cerebral aneurysm treatment with nickel-containing flow-diverting stents, there were no apparent allergic reactions despite the lack of periprocedural prophylactic treatment with steroids or antihistamines. Our series further supports these results, because we found no evidence of allergic or other adverse clinical reactions among our patients. Moreover, we found that, in all 6 patients with angiographic follow-up, complete obliteration of the vascular lesion was demonstrated without adverse sequelae.

Although our results suggest that neuroendovascular treatment with nickel-containing devices may be safe in patients with nickel or other metal allergies, other authors have reported some cases of adverse effects possibly attributable to allergic reactions to metal. Fujii et al¹⁴ reported a case of delayed in-stent stenosis in a patient with a cobalt allergy who was treated with a nickel-containing flow-diverting stent. Other authors have reported cases of diffuse cerebral edema with seizures or focal neurologic deficits after placement of a nickel-containing device.^{13,15} However, the exact etiology in these cases has not been fully elucidated. Fortunately, the patients in these cases were successfully treated with systemic steroids, which resulted in radiologic and clinical resolution of their symptoms.^{13,15} Similarly, other authors have reported radiographic sequelae, including foci of MR imaging enhancement in the catheterized territory that developed in the weeks after the procedure and responded to steroid treatment.^{16,20,21} Together, these findings suggest that a delayed, steroid-responsive hypersensitivity-like reaction is possible after endovascular treatment; however, the exact etiology remains to be fully elucidated. On the basis of our results and those of other authors, we believe that there is a low relative risk of severe allergic reactions after treatment with nickel-containing neuroendovascular devices.

However, precautionary steps to help mitigate any potential risk should be considered. We did not pursue nickel allergy patch testing for the patients in our series who reported having a nickel allergy before their treatment with a nickel-containing device; however, performing a patch test before an elective treatment may be a reasonable approach. Other authors recommend this strategy to enable better patient counseling and to provide an opportunity to consider treatment alternatives.²² However, others have reported that patch testing was of very limited clinical utility for patients undergoing endovascular treatment.¹¹ The incidence of nickel hypersensitivities is likely underreported in retrospective

studies. To better address this area of concern and to assist in future analyses and patient counseling, we have implemented a policy of explicitly asking all patients about any potential metal allergies or hypersensitivities when they are scheduled to undergo an elective endovascular treatment in which a nickel-containing device is part of the treatment plan.

One potential reason for the lack of frequent consequential adverse reactions after placement of nickel-containing cerebrovascular stents in patients with reported nickel allergies is that the commonly used neurovascular stents do not actually release nickel ions. The release of nickel ions is necessary to induce a nickel hypersensitivity response via immune cell activation. Recent in vitro work by Vanent et al²³ determined that commonly used nickel-containing cerebrovascular stents—including those used in our series—do not actually release nickel ions. These findings correlate with our clinical results because the lack of free nickel ion release from the stents would preclude a clinical hypersensitivity response. Taken together, these results suggest that patients with a nickel allergy who require endovascular treatment for cerebrovascular lesions may be safely treated with nickel-containing stents. This conclusion is supported by the general observation that the percentage of patients with adverse effects after treatment with nickel-containing devices (generally reported as markedly <10%^{24–27}) is notably less than the estimated prevalence of nickel allergy or hypersensitivity within the general population (10%–15%).²⁸ However, neither our results nor the previously reported data preclude a causal relationship between a metal or nickel allergy and any adverse reaction. Therefore, to more comprehensively address the relative risk and possible causation, larger prospective databases are required that systematically document allergy status and identify potential clinical and imaging sequelae.

Our study was limited by its retrospective nature and the small patient cohort. Limitations included a lack of rigid standardization of clinical and radiologic follow-up timing, technique, and granularity. These limitations may have obscured minor clinical or radiologic sequelae. Furthermore, we ascertained the presence of a cutaneous metal allergy from a retrospective chart review rather than from formal dermatologic allergy testing. Although we review allergies for all patients as part of our standard inpatient and clinic history and physical, it is possible that the sensitivity and specificity of this methodology produce both false-positive and false-negative results. It is important to note that, in light of population statistics, the number of patients with reported nickel or other metal allergies or hypersensitivities in our study likely underestimates the actual number of patients with such hypersensitivities. Future prospective studies are warranted that are designed to describe the safety and efficacy of nickel-containing devices in neurosurgery, the potential role of patch testing for nickel allergies, and the possible benefit of prophylactic treatment.

CONCLUSIONS

In this small case series, the endovascular treatment of cerebrovascular lesions with a nickel-containing device in 7 patients with documented nickel or other metal allergies did not result in any adverse outcomes and was safe and effective overall. Further research in this area is warranted.

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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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