Neurological Changes with Abnormal Brain Reactivity Following Coiling of Cerebral Aneurysm. Possible Reactivity to Endovascular Devices and Material?

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Summary
A 65-year-old woman presented with headaches and underwent coiling of an unruptured posterior communicating artery aneurysm. A few days later, she developed left-sided weakness. MRI revealed enhancing white matter lesions in the ipsilateral hemisphere. The patient underwent extensive work-up and was treated with a prolonged course of immunosuppression.

Thirty months postcoiling, the patient had resolution of all clinical symptoms. Imaging revealed improvement in the white matter changes. Six months after tapering the immunosuppressants, follow-up MRI showed interval development of new white matter lesions. The patient was restarted on immunosuppression and was clinically stable at 47 months postcoiling.

We present a case with abnormal brain reactivity following elective coiling of an aneurysm, with a review of clinical outcome at 47 months. We discuss the radiological findings, along with management of this phenomenon, and review the literature.

Background
Unruptured cerebral aneurysms are currently treated using either endovascular or microsurgical techniques. After the emergence of the international subarachnoid aneurysm trial (ISAT) results, coiling has gained increased popularity in the treatment of intracranial aneurysms [1,2]. As a result, the field has witnessed a rapid improvement in the design and materials of endovascular devices, with little understanding of rare pathologies associated with this relatively new and ever-changing treatment modality.

Standard coils are highly engineered wires mainly composed of platinum (92%) and tungsten (8%). These coils are available in both pure and alloy forms, with potential for allergic reactions to these materials whether in pure or alloy form [3]. In addition, catheters can contain polyvinylpyrrolidone (PVP), which can embolize and elicit an inflammatory response. As this field continues to evolve, raising awareness of these reactions and sharing similar events is essential to identify the insulting agent and to draw efficient management strategies.

Case Presentation
A 65-year-old woman presented with headaches. Medical work-up was noncontributory except for a slightly elevated sedimentation rate (ESR) at 34. Magnetic resonance imaging (MRI) of the brain showed few punctate areas of periventricular T2 and fluid-attenuated inversion recovery (FLAIR) signal abnormalities. Imaging revealed a 9 mm right posterior communicating (PCOM) artery aneurysm. The patient continued to have worsening of headaches and underwent workup for CNS vasculitis. Cerebral angiogram confirmed the presence of a 9 × 6 mm right PCOM aneurysm with no other significant findings (Fig. 1). Options were reviewed, and plan was made to proceed with aneurysm coiling. A 5 French Cook Shuttle Select guiding sheath was used...
with a JB1slip-catheter (Cook Medical, Bloomington, IN, USA) that was advanced into the right internal carotid artery, and the aneurysm was coiled with platinum bioactive cerecyte coils (Codman, Raynham, MA, USA) through an SL-10 microcatheter (Stryker neurovascular, Fremont, CA, USA). The groin access was closed with a 6 French Angio-Seal (St. Jude Medical, Minnetonka, MN, USA).

The patient tolerated the procedure well and was discharged home with no events. Four days later, she presented with left-sided weakness that was confirmed on exam. Imaging showed interval development of extensive nonenhancing hyperintense FLAIR and T2 signal abnormalities with mass effect involving the right hemisphere, likely representing an inflammatory process (Fig. 2). ESR was 108 and cerebral spinal fluid (CSF) analysis showed elevated white blood cell (WBC) and proteins. Flow cytometry and cytology were negative. Venereal disease research laboratory (VDRL) testing was negative. Cultures for bacterial, fungal, and acid-fast bacilli (AFB) were negative. The patient received a course of steroids over six weeks with complete resolution of her symptoms. Following a steroid taper and within two weeks, she had recurrence of her symptoms. Repeat imaging showed diffuse white matter changes in the frontal and parietal lobes, with relative sparing of the cortices (Fig. 3). During the same period, she had an aseptic inflammatory process involving the right groin access site that cleared by the fourth week without antibiotics.

Initially, an allergic reaction to polyglycolic/polyactic acid (PGLA) material within the coil was suspected, as the patient also had a reaction at the groin site, and this was the common element between bioactive Cerecyte coils and the absorbable suture in the Angio-Seal. Due to a prior history of nasal ulcer and perforation, concern was also raised about Wegener's granulomatosis and the patient underwent a nasal biopsy and was maintained on steroids. The biopsy results were negative for Wegener’s granulomatosis. Follow-up MRI at four months showed improvement in the FLAIR abnormalities (Fig. 4).

She remained clinically stable during a 12-month course of treatment with steroids and mycophenolate. However, as her steroid dose was tapered down, her 15-month MRI showed interval worsening of FLAIR abnormalities, with scattered areas of enhancement, especially in the right temporal lobe (Fig. 5). MRI spectroscopy showed a prominent choline to creatinine peak, with somewhat depressed N-acetyl aspartate (NAA). Lymphoma and other pathologies were considered, and the patient refused brain biopsy.
The steroids and mycophenolate were used for a prolonged period of time. When we attempted to wean her steroids at 22 months postcoiling, she had recurrence of her symptoms, necessitating resumption of these medications. Repeat imaging at 27 months showed near resolution of the changes in her temporal lobe and marked reduction in her frontal lobe abnormalities (Fig. 6).

She had a series of allergy tests and tested positive for cobalt allergy. We also did a patch cover skin test with a sample coil and PGLA from a disassembled cerecyte coil, and there was no inflammatory response. The hypothesis of possible allergy to coil material was initially entertained but could not be confirmed or eliminated as the patient was on a low dose of steroids. Once the patient was completely off of immunosuppressive therapy, she had implantation of a bare platinum coil, a Cerecyte coil, and PGLA in the forearm. The implants were explanted 2.5 weeks later with no reaction to the materials (Fig. 7).

She remained asymptomatic, and at 38-month follow-up, brain MRI showed two new areas of enhancement in the right periventricular area and the right frontal lobe (Fig. 8).

Treatment with mycophenolate was reinstituted and follow-up MRI at 42 months showed a smaller right posterior periventricular lesion and resolution of the lesion within the frontal lobe (Fig. 9).

The patient is now more than 47 months postcoiling and is symptom-free but is still on mycophenolate therapy. She is clinically stable, and the most recent MRI of the brain showed no new white matter lesions. However, significant loss of brain substance was noted in the right hemisphere.

**Discussion**

Studies have shown that morbidity following endovascular coiling of aneurysms ranges from 9.8% to as high as 23.7% [1,4,5], and the 1-year mortality rate has been reported to range from 3.4–15% [1,3,5]. Most of these complications are access related or thromboembolic in nature. Inflammatory reactions to endovascular devices, such as allergy or granulomatous reactions, are not frequent.

Metal allergies have been reported in a wide-range of surgical subspecialties. A possible mechanism for this occurrence is through delayed hypersensitivity, a cell-mediated response to an allergen. Delayed type hypersensitivity is so named, because the reaction usually takes 3–4 days to develop, unlike the other hypersensitivity reactions. Within the neurosurgery literature, reports have focused on allergy related to metal clips. Ross et al. described intense pruritus in a patient with a clip containing cobalt and nickel [6]. The same metals, among several others, are also present in trace amounts in standard coils. Typically, diagnosis of a cobalt allergy
consists of examining the skin for a rash and patients complaining of severe pruritus over the entire body. While cobalt allergy commonly presents as a local rash or contact dermatitis, the neurosurgical patient can present with a systemic reaction, as the allergen has direct access to the circulatory system. This is best described in the case of systemic nickel allergy syndrome, where patients can have eczematous, vasculitic, mucosal, respiratory, urticarial, or gastrointestinal reactions. The diagnosis can be confirmed with a positive patch test, and medical management includes the use of oral corticosteroids and antihistamines [7].

PGLA coils are designed to reduce aneurysm recurrence by reducing the residual volume and allowing inflammation-induced scarring within aneurysms. Progressive loss of tensile strength and the eventual absorption of PGLA occur through hydrolysis, where the co-polymer degrades to glycolic and lactic acids, which are subsequently absorbed and metabolized into the body. The
PGLA component elicits a minimal acute inflammatory reaction in tissue and an ingrowth of fibrous connective tissue. In vivo studies indicate that absorption of PGLA is essentially complete between 60 and 90 days. It is certainly possible that PGLA in coils may produce an exaggerated inflammatory reaction, which may lead to a similar reaction in the brain. In previous reports documenting similar reactions in two cases, patients underwent coiling of posterior circulation aneurysms using PGLA coils, with symptoms and radiographic changes noted.

Figure 4. Four months postcoiling. FLAIR-sequenced MRIs of the brain showing a marked reduction in FLAIR abnormalities with very mild volume loss/atrophy in the right hemisphere.

Figure 5. Fifteen months postcoiling. FLAIR-sequenced MRIs of the brain showing new abnormal hyperintense lesions with prominent sulci in the right hemisphere related to volume loss.
approximately one month later [8]. Both patients had white matter changes confined within the vascular territory of the coiled aneurysm and a negative work-up for inflammatory and infectious processes, with no elevations in ESR. The report theorized that the white matter changes and neurologic symptoms were due to exaggerated postoperative extravascular inflammatory reactions to the PGLA coils [8]. In terms of outcomes, both clinical and MRI changes did improve significantly within four to five months with conservative management. In our patient, neurological symptoms persisted much longer and required a prolonged course of immunosuppres-

Figure 6. Twenty-seven months postcoiling. Flair-sequenced MRIs of the brain showing resolution of the hyper intense signal changes in the right temporal lobe with a marked reduction of the signal changes in the right frontal lobe. Also note the prominence of the sulci in the right hemisphere, likely related to the volume loss mentioned in Figure 5.

Figure 7. Patch cover test. (Left) Implantation of bare PGLA (a), Cerecyte coil (B), platinum coil (C). (Right) Same coils 2.5 weeks later with no inflammatory response noted.
Further, follow-up MRI showed persistent changes with the development of brain atrophy. We also considered the possibility that these reactions could be related to the coil materials, as the changes on MRI with the enhancing nodules were very similar to the aforementioned report [8]. Indeed, both patients in the aforementioned report and our patient had enhancing lesions in the same vascular tree that was noted following aneurysm treatment. We also entertained the possibility that this reaction could be related to widespread embolization of hydrophilic gel coating of coils. As described in a previous case report [9], deposition of polymer material from coils was noted in unpredictable areas, leading to granulomatous reactions and multiple infarcts, which ultimately led to death. Embolization of coil material was confirmed by autopsy, which showed deposition of gel material in the areas of infarct. In our case, the possibility of an allergic reaction to PGLA coils is remote, as the patient had an investigational implantation of the coil components with no allergic reaction. Although it is possible that the patient was desensitized over time to the inciting agent, this reaction is likely related to the endovascular treatment, as these reactions have been confined to the same vascular territory in all cases and may be related to debris from endovascular devices released during the procedure.

A recent case series also described deposition of polyvinylpyrrolidone (PVP) in small vessels of patients who developed intraparenchymal hemorrhage after use of pipeline embolization device [10]. A Cook shuttle sheath was used in all these cases to stabilize the endovascular construct. In the present case, a Cook Shuttle was also used, but the reaction was quite different and could be related to materials released from the catheters and/or wires of the endovascular system. Although the insulting agent remains indeterminate, to our knowledge this is the first report where an allergic reaction to coils

Figure 8. Thirty-eight month follow-up, (a) FLAIR. (B) FLAIR. (C) T1 postgadolinium. (D) T1 postgadolinium. (a, B) FLAIR-sequenced MRIs of the brain showing new right posterior periventricular hyper intense lesion. (C, D) T1 postgadolinium showing new areas of enhancement in the right frontal lobe (C) and the right posterior periventricular area (D).
was ruled out by implantation of different coil components.

**Conclusion**

This report describes the case of abnormal brain reactions with significant neurological side effects following coiling of an intracranial aneurysm. The patient was treated with immunomodulation for a prolonged period of time and became dependent on this treatment to maintain the stability of her disease. Based on our interpretation of previous cases [8] and our case, the reaction is likely related to detached material from endovascular devices, as the enhancement was confined to the same vascular tree of the treated aneurysm. Although the insulting agent remains unknown, the reaction is not likely to be related to the PGLA coils, as the patient had no reaction to implanted coil materials and PGLA while off immunosuppression.

**References**