considered as another option. In patients with type IV Ehlers-Danlos syndrome, if surgery is necessary, targeted gentle surgical technique by experienced surgeons is important. Nevertheless, even with these management changes, the patient may have still had a persistent tuboovarian abscess with a complicated hospital and postoperative course secondary to her underlying disease and tissue fragility.

In conclusion, although vascular Ehlers-Danlos syndrome is a rare collagen disorder, it is important to be aware of this disorder because it is often difficult to diagnose unless one is mindful of the characteristic history and examination findings noted in this case. Knowledge of this diagnosis can be critical to patient care in gynecology. The principles to use are: 1) conservative management if possible; 2) avoidance of or minimal surgery to avoid excessive damage to delicate tissues; and 3) use of a multidisciplinary approach to care.

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Anti-*N*-Methyl-Aspartate Receptor Encephalitis in Identical Twin Sisters

Role for Oophorectomy

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BACKGROUND: Anti-*N*-methyl-aspartate receptor encephalitis is a potentially fatal form of encephalitis and frequently associated with ovarian teratomas. Surgical removal of ovarian teratomas improves clinical outcome, but it is unclear whether bilateral salpingo-oophorectomy for normal-appearing ovaries is of clinical benefit.

CASE: Our report describes a unique clinical scenario of identical twin sisters with anti-*N*-methyl-aspartate receptor encephalitis. Neither patient responded to immunosuppressive therapy. Imaging studies showed normal-appearing ovaries. The first twin continued on medical therapy only and died of the disease. The second twin underwent a bilateral salpingo-oophorectomy followed by gradual recovery.

CONCLUSION: Based on our experience in two genetically identical individuals, we suggest considering the removal of normal-appearing ovaries in patients with anti-*N*-methyl-aspartate receptor encephalitis who fail to respond to medical treatment.

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Anti-*N*-methyl-aspartate (NMDA) receptor encephalitis is a severe form of autoimmune encephalitis with a high mortality rate.[1] Patients usually present with flu-like symptoms, which are followed by psychiatric and neurologic signs such as hallucinations, seizures, dyskinesias, ataxia, and hypoventilation.[2] The differential diagnosis includes other forms of encephalitis, stroke, or epilepsy. The medical treatment of patients with anti-NDMA receptor encephalitis consists of immunosuppressive therapy with agents like cyclophosphamide or rituximab, plasmapheresis, and frequently mechanical ventilation and cardiac support.[3] *N*-methyl-aspartate receptor is a glutamate receptor that is expressed in brain tissue and activated by glutamate and glycine. Glutamate is the most abundant excitatory neurotransmitter in the brain.[4] Expression of NMDA receptor is predominantly found in the forebrain, the hypothalamus, the pituitary, and the limbic system. *N*-methyl-aspartate receptor signaling plays an important role in synaptic plasticity, which is the ability of synapses to change their strength, dendritic

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sprouting, and hippocampal long-term potentiation involved in memory and learning functions.[1] Dysfunction of this receptor has been linked to schizophrenia and dementia.[2]

In patients with anti-NMDA receptor encephalitis, antibodies to the NMDA receptor subunits NR1 and NR2 are found in the cerebrospinal fluids and serum. Although the exact mechanisms that cause this disease are still under investigation, anti-NMDA receptor antibodies might cause glutamatergic hyperactivity and subsequent hyperexcitation. Magnetic resonance imaging of the brain shows mild contrast enhancement in 50% of cases and atrophy in later stages.[2,5] Approximately 80% of patients with anti-NMDA receptor encephalitis are young females of reproductive age.[2,5,6] Furthermore, approximately 40–60% of reported cases are associated with ovarian teratomas, and surgical removal of these teratomas has been shown to accelerate the recovery of patients.[1–3,5] Interestingly, studies have demonstrated that NDMA receptor can be aberrantly expressed in ovarian teratoma tissue.[5] It has therefore been hypothesized that the generation of anti-NMDA receptor antibodies might be induced by ectopic NMDA receptor expression in ovarian teratomas.[1] Although the therapeutic role of surgical removal of ovarian teratomas in patients with anti-NMDA receptor encephalitis is rather well established, the effect of removing normal-appearing ovaries on the disease course is unclear.

CASE 1

Patient 1 is a 27-year-old Filipina-American woman (gravida 0) who initially developed flu-like symptoms with general malaise, fatigue, headaches, vomiting, and photophobia. She subsequently experienced generalized tonic–clonic seizures and was admitted to the intensive care unit with the diagnosis of infectious encephalitis of unknown origin. The cerebrospinal fluid tested negative for herpes simplex virus, cryptococcal antigen, and West Nile virus. In addition, analysis of rheumatoid factor, antinuclear antibody, antimyeloperoxidase antibody, proteinase 3 antibody, antidouble-stranded DNA antibody, cytoplasmic antineutrophil cytoplasmic antibody, and perinuclear antineutrophil cytoplasmic antibody was negative. An electroencephalogram showed high-amplitude rhythmic delta activity suggestive of seizure activity. The patient developed choreiform movements and required intubation for continuous sedation. A brain biopsy showed reactive changes including microglial activation and multifocal gliosis. Cerebrospinal fluid analysis showed positive anti-NMDA receptor antibody titers. The patient was treated with immunosuppressive therapy including prednisone, plasmapheresis, and rituximab. The serum tumor markers CA19-9 (56 units/mL [0–35]) and CA125 (71 units/mL [0–35]) were both elevated suggesting the possible presence of tumor disease with paraneoplastic syndrome. Pelvic ultrasound, magnetic resonance image, positron emission tomographic, and computed tomography scans did not show any abnormalities on the ovaries, uterus, or extrapelvic organs. Immunosuppressive medical therapy was continued without significant improvement and finally death of the patient, likely as a result of sudden cardiac arrhythmia. The autopsy showed normal ovaries without evidence of teratoma.

CASE 2

Patient 2 is the 27-year-old identical twin of patient 1. Her initial symptoms developed only days after her twin sister had died of the disease and included fatigue, fever, nausea followed by altered mental status and finally seizures. The patient's diagnostic work-up included a negative analysis of the cerebrospinal fluid for an infectious origin but positive titers for anti-NMDA receptor antibodies. Similar to her sister's treatment, the patient was treated with immunosuppressive therapy including cyclophosphamide, rituximab, prednisone, and plasmapheresis. Elevated levels of CA19-9 (133 units/mL [0–37]) and CA125 (99 units/mL [0–35]) again suggested the possible presence of a paraneoplastic syndrome. Imaging studies including pelvic ultrasound and positron emission and computed tomography scans did not show any abnormalities of the ovaries. As a result of the lack of response to 4 weeks of medical treatment, the patient underwent a laparoscopy, which showed normal-appearing abdominal and pelvic organs. A bilateral salpingo-oophorectomy was performed based on the rationale that the ovaries might contain an ovarian microteratoma not visible on imaging studies. The final pathology revealed histologically normal ovaries and fallopian tubes. After surgery, the patient continued on immunosuppressive therapy, and her symptoms gradually improved. She finally was discharged to a rehabilitation facility in stable condition. She has been monitored as an outpatient in both the neurology and gynecology clinics and, except for slight memory impairment, is fully functional.

COMMENT

Anti-NMDA receptor encephalitis has been recognized as a form of potentially fatal autoimmune encephalitis.[2] Previously published case series have shown that the surgical removal of ovarian teratomas early in the disease process leads to a faster recovery, lower severity of symptoms, and a lower rate of recurrence.[1–3,5,6] In contrast, in the absence of ovarian teratomas, patients maintain high antibody titers, show a delayed response to immune therapy, and frequently require second-line immunotherapy.[2,5] Additionally, the risk of relapse is

significantly higher in patients without tumor.[6] These patients therefore do present an even greater clinical challenge and the best therapeutic strategy including bilateral salpingo-oophorectomy has yet to be determined.[7] In our two cases, the second twin sister clinically improved after the oophorectomy, but given the multimodality treatment regimen with aggressive medical management, the contribution of the surgical procedure to the outcome is uncertain. It is however interesting to note that 50% of patients with anti-NMDA receptor encephalitis do not show any evidence of ovarian teratomas on imaging studies and that the incidence is even lower (9%) in girls younger than 14 years.[2,3,6] The presence of ovarian microteratomas that are radiologically occult and are only identified through histopathologic examination has been described.[8]

Our two cases of anti-NMDA receptor encephalitis are unique as a result of the identical genetic background for both patients with a drastically different clinical outcome. These cases do not prove an association of anti-NMDA receptor encephalitis with normal ovarian tissue until investigations regarding the underlying biological mechanisms provide further insight. Because this form of encephalitis is diagnosed primarily in female patients and is being diagnosed with increasing frequency, gynecologists should be aware of the severity of this disease and the potential effect of ovarian surgery in patients for whom medical therapy is not successful.

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