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CASE REPORT

‘Benign’ ovarian teratoma and N-methyl-D-aspartate receptor (NMDAR) encephalitis in a child

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Abstract N-methyl-D-aspartate receptor (NMDAR) encephalitis is a life-threatening paraneoplastic neuropsychiatric encephalitis that predominantly affects young women and has a strong association with ovarian teratomas. Removal of the ovarian teratomas improves the prognosis and decreases the risk of recurrence. We present an 11-year-old girl with NMDAR encephalitis with small bilateral teratomas not initially appreciated on abdominal CT or pelvic MRI. A 12-mm teratoma was identified in the right ovary and a 7-mm teratoma was identified in the left ovary on US follow-up at 5 months. Intraoperative sonography was used to localize the teratomas for excision. In NMDAR encephalitis, the ovarian teratomas can be very small, particularly in children, and easily missed on cross-sectional imaging. Awareness of the association of NMDAR encephalitis and ovarian teratomas will improve the diagnostic accuracy and imaging interpretation. Periodic sonography and MRI might be warranted in children if the initial study is negative.

Keywords NMDA · NMDAR encephalitis · Paraneoplastic encephalitis · Children · MRI · US

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Introduction

N-methyl-D-aspartate receptor (NMDAR) encephalitis is a potentially lethal paraneoplastic condition that has a strong association with ovarian teratomas [1–5].

NMDAR encephalitis is a recently recognized condition caused by antibodies to N-methyl-D-aspartate (NMDA) receptors that results in a neuropsychiatric encephalitis [2]. Typically, patients present after a prodromal illness followed by a psychotic episode that includes confusion, emotional disturbance, cognitive decline and seizures [3, 5, 6]. Later in the illness, patients might develop choreoathetoid movements, tachycardia or bradycardia, decreased level of consciousness and hypoventilation requiring ventilation [3, 5, 6]. Approximately 1% of ICU encephalitis admissions are caused by NMDAR encephalitis [7]. Although patients might gradually recover, in one study 37 out of 44 patients developed a severe disability [6] and in another study 25 out of 100 patients sustained a severe deficit or died [3].

NMDAR encephalitis is much more common in young adult women than men, with a reported frequency of 70% and 91% and a median age of 22 years and 23 years in two series [3, 6]. Ovarian teratomas have been identified in 26–60% of female patients with NMDAR encephalitis [3, 6]. An immature testicular teratoma was also demonstrated in 1 out of 9 male patients with NMDAR encephalitis [3]. Teratoma incidence in NMDAR encephalitis is less frequent in children, occurring in only 1/11 (9%) in one study in

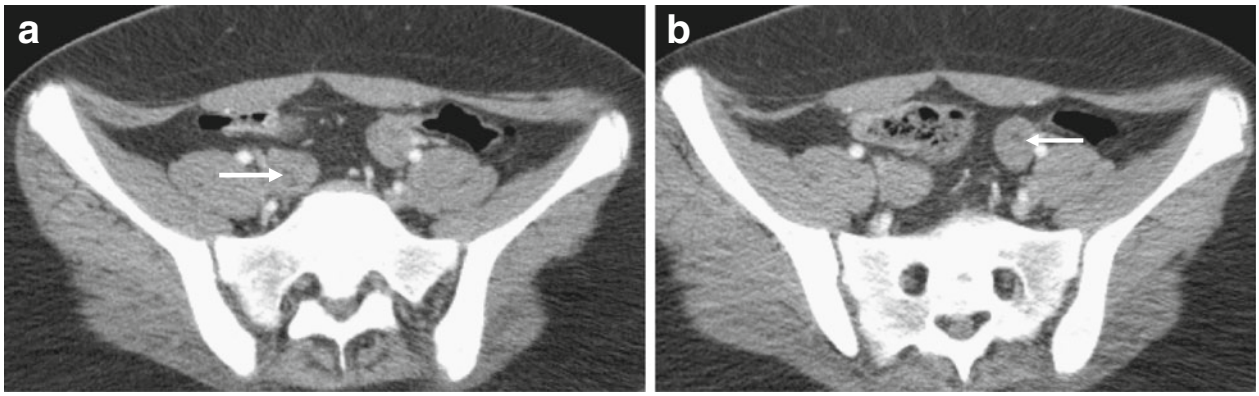

Fig. 1 Axial reconstruction CT through the pelvis demonstrates (**a**) a subtle lesion with decreased attenuation evident on review of the right ovary (*arrow*) and (**b**) left ovary (*arrow*)

children younger than 14 years [4]. Patients with a teratoma tend to do better after removal of the tumor than those with NMDAR encephalitis who do not have a tumor [2, 6].

We present an 11-year-old girl with NMDAR encephalitis whose clinical presentation and neurological manifestations have previously been reported [8]. This review focuses on the imaging findings of small bilateral ovarian teratomas not initially appreciated on CT and MR imaging of the pelvis.

Case report

An 11-year-old girl with no medical history presented with generalized tonic clonic seizures and an altered mental state. Her initial symptoms included headache, neck pain and hypersomnia for approximately 1 week. A CT performed at the time was normal. Lumbar puncture revealed a mild pleocytosis and mildly elevated protein. The girl remained hospitalized for 3 weeks with ongoing seizures, personality change and periods of catatonia and bradykinesia. Serial brain MRIs revealed increased cortical signal in the right superior frontal gyrus and subtle bilateral inferior medial gyrus cortical changes [8].

After 3 weeks of hospitalization, the girl's parents elected to transfer her to our institution for a second opinion. A PET scan showed focal hypermetabolism in the right frontal lobe correlating to the cortical signal abnormality noted on MRI [8]. A CT of the chest, abdomen and pelvis was performed to assess for an occult malignancy. This was initially interpreted as normal apart from a paratubal cyst, but on review there were subtle foci of fatty attenuation in the left and right ovaries (Fig. 1). On a subsequent MRI without fat-sensitive sequences, the two small ovarian lesions were interpreted as hemorrhagic cysts (Fig. 2). Serum NMDAR antibodies were negative, but the CSF was strongly positive for antibodies to the NR1/NR2 subunits of the NMDAR. Prior to identifying the anti-NMDAR antibodies, the girl was started on high-dose intravenous methylprednisolone. She was then treated with plasma exchange for five sessions on alternating days. At the end of this therapy, the girl was seizure-free and the choreoathetoid movements had ceased. She was discharged 8 weeks after her initial onset of symptoms.

Three months after discharge, an outpatient pelvic US exam demonstrated bilateral ovarian small echogenic lesions without posterior acoustic enhancement (Fig. 3). A repeat MRI of the ovaries with fat saturation confirmed the

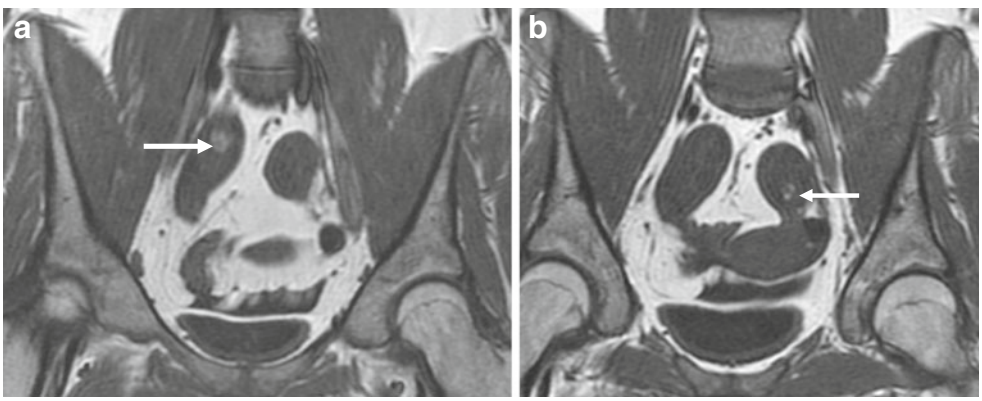

Fig. 2 Coronal non-fat-saturated T1-W MR images through the pelvis demonstrate (**a**) a lesion with increased T1 signal within the right ovary (*arrow*) and (**b**) left ovary (*arrow*)

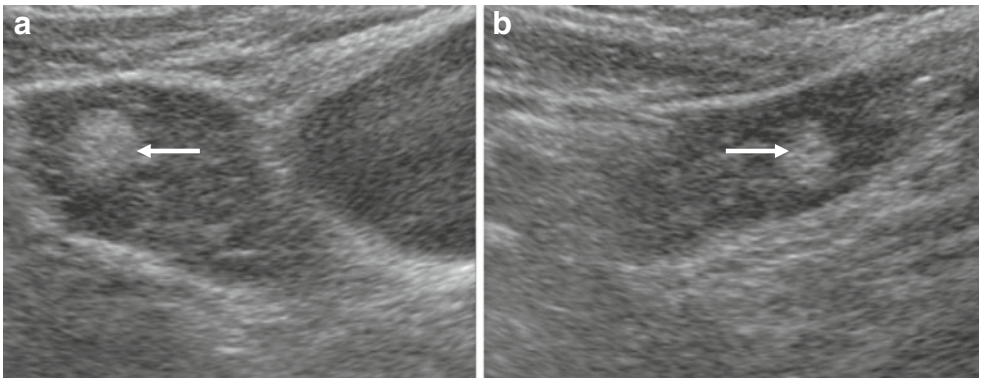

Fig. 3 US of the right and left ovaries demonstrates (**a**) a 12-mm well-defined echogenic lesion in the right ovary (*arrow*) and (**b**) a 7-mm well-defined echogenic lesion in the left ovary (*arrow*). The findings were concerning for small ovarian teratomas, given the patient's history of NMDAR encephalitis

diagnosis of ovarian teratomas (Fig. 4). Approximately 6 months after the girl's initial onset of symptoms, a laparotomy and US-guided excision of the ovarian lesions was performed. Pathology confirmed bilateral ovarian teratomas. These contained mature ectodermal elements including squamous epithelium, hair follicles, sebaceous and apocrine glands and mesodermal elements including mature adipose tissue, small nodules of hyaline cartilage and pancreatic-type glandular tissue. No neural elements were identified and an immunohistochemical stain for glial fibrillary acidic protein (GFAP) was negative. The margins were focally positive, suggesting possible incomplete excision. No immature elements or malignant germ cell tumor was identified.

At a follow-up 8 months after the initial presentation, the girl was seizure-free and had been successfully weaned off anticonvulsant medication. She has returned to school and retained pre-morbid cognitive function and behavior.

Discussion

The case presented highlights some of the typical features of NMDAR encephalitis associated with ovarian teratomas and the potentially subtle findings of ovarian teratomas in children.

The pathogenesis of NMDAR encephalitis in patients with ovarian teratomas is thought to be related to antigenic stimulation from the NMDAR in ectopic nervous tissue contained in teratomas [2]. Infection can cause immune activation and lead to increased permeability of the blood–brain barrier [3]. The antibodies to the NMDA receptors cause inhibition of the NMDA receptors in the forebrain, hippocampus, amygdala and hypothalamus contributing to the schizophrenia-like symptoms [5].

The typical patient presents with a characteristic clinical picture that is preceded by a prodromal illness followed by seizures, a psychotic acute phase and then an unresponsive and hyperkinetic phase [5]. MRI brain findings are often limited in NMDAR encephalitis without significant correlation with the patient's symptoms [3]. In this case, the diagnosis of ovarian teratomas was made with US after the acute episode and the teratomas were confirmed with an MRI of the pelvis with fat-sensitive sequences.

Because of their small size, the ovarian teratomas were not initially appreciated on CT or MRI. Similar findings were found by Iizuka [5] in a study of four patients who were retrospectively diagnosed with NMDAR encephalitis several years after their acute illness. In this study, once testing was available, the stored CSF and serum samples were found to be positive for NMDAR antibodies in patients who had been undiagnosed but had a typical clinical presentation. Once the

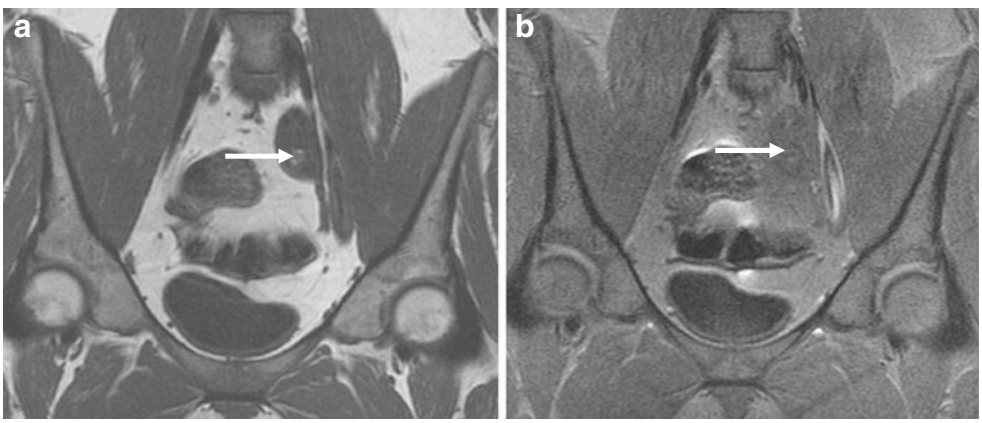

Fig. 4 Repeat coronal T1-W MR images of the pelvis with and without fat saturation demonstrate (**a**) an increased T1 signal lesion in the left ovary (*arrow*) and (**b**) reduced signal on the fat-saturation image (*arrow*)

diagnosis was made, follow-up US demonstrated ovarian teratomas in three of the four patients at a time interval of between 4 years 1 month and 7 years 3 months after the initial illness. In this study, retrospective review of prior imaging revealed a 2-cm ovarian cyst evident on a CT performed at the time of the initial symptoms. This had grown to 6 cm at the time of the follow-up study. Removal of the tumors confirmed the diagnosis of a cystic teratoma in all three patients [5].

The small size of the ovarian teratomas in our patient made the initial diagnosis difficult. Children typically are reported to have a lower incidence of teratomas than adult patients with NMDAR encephalitis [4, 6]. This might be a result of the small size of the lesions making them harder to identify in young children [6]. The median size of 53 teratomas diagnosed in the largest series, which included both adults and children, was 6 cm (range 1 cm to 22 cm) [3] compared to our case where the teratomas were 12 mm and 7 mm in diameter. As in our case, 8 of the 53 patients in this series had bilateral teratomas [3]. In this series of 100 patients, 7 patients had an exploratory laparotomy looking for occult tumors but only 1 tumor was found [3]. In our case, the intraoperative sonogram helped to localize the small teratomas that were occult to visual inspection.

The ovarian teratomas were confirmed histologically in our patient, but neural elements were not identified. This is not typical. In the study by Dalmau [2], all the teratomas with a pathological diagnosis had nervous tissue and the 25 examined for NMDA receptors were all positive [2]. It is possible that microscopic neural elements were missed because of sampling variability in our case. NMDAR encephalitis has also been reported with other tumors such as lung cancer and in patients without a tumor [3, 4, 6]. The cause of the immune mechanism in NMDAR encephalitis in the absence of a tumor is unknown. Possible theories include inability of imaging procedures to detect small tumors, inadequate imaging follow-up or other unknown immunological triggers [3, 4, 6].

The child in our study had made substantial improvement after immunosuppressant therapy and plasma exchange prior to removal of the teratomas. It has been shown that patients with tumor removal have a better outcome and relapse less often than patients in whom no tumor is found [2, 3, 6]. Although the disorder might resolve without tumor resection, the serious consequences of the illness, including death, support tumor removal [5].

In summary, NMDAR encephalitis is a life-threatening neuropsychiatric encephalitis that predominantly occurs in young women and has a strong association with ovarian teratomas [1–5]. Removal of the ovarian teratoma in patients with NMDAR encephalitis improves the patient's prognosis and decreases the risk of recurrence [2, 3, 6]. This case illustrates that the teratomas can be very small, particularly in children, and easily missed on cross-sectional imaging. We hope awareness of the association of NMDAR encephalitis and ovarian teratomas will improve the diagnostic accuracy and imaging interpretation of what appear to be benign ovarian findings. US is the screening modality of choice and periodic US imaging might be warranted in children if the initial study is negative. MRI, including T1-W images and T1-W images with fat saturation, is recommended to clarify equivocal US findings or to evaluate the ovaries if they are not clearly visualized with US.

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