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Anti-NMDA receptor encephalitis with the initial presentation of psychotic mania

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ABSTRACT

We report a 16-year-old girl with suspected psychotic mania, who subsequently developed amnesia, catatonia, oro-lingual dyskinesia, consciousness disturbance, seizure and respiratory failure. Repeated studies of the cerebrospinal fluid (CSF), viral culture and serology, brain MRI, single photon emission CT scan, and autoimmune profiles were all normal. She was finally diagnosed with anti-N-methyl D-aspartate receptor (NMDAR) encephalitis based on the positive finding of NMDAR antibodies in CSF. Her abdominal CT scan showed no detectable malignancy and pulse steroid therapy failed to have any effect. After administration of intravenous immunoglobulin her consciousness improved gradually. Anti-NMDAR encephalitis, with a characteristic neuropsychiatric syndrome, predominantly affects females with an ovarian tumor and is frequently misdiagnosed as a psychiatric disorder. Immunotherapy and eradication of associated malignancy are the main treatment strategies. Early recognition and early intervention of the disease should improve the outcome.

1. Introduction

Autoimmune encephalitis (AE) can be divided into two broad groups according to the location of the antigens. AE associated with antibodies to intracellular neuronal antigens, including anti-Hu, anti-CV2 and anti-Ma2, usually have an underlying malignancy (small cell lung cancer, breast, and testicular cancer). AE associated with antibodies to neuronal surface antigens, including the voltage-gated potassium channel, and N-methyl-D-aspartate receptors (NMDAR), are usually more responsive to immunotherapy and involve malignancy less commonly.[1,2] NMDAR are highly expressed in the forebrain, limbic system, and hypothalamus.[3] Anti-NMDAR encephalitis was recognized recently.[4] We present a patient with anti-NMDAR encephalitis with an initial manifestation of psychotic mania.

2. Case report

A 16-year-old girl, with no known physical or psychiatric illness, was brought to our emergency department (ED) presenting with irritability, hyperactivity and a decreased need for sleep. Four days prior to the ED visit, she burst out laughing and sang loudly at

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inappropriate times. She claimed that she heard music and someone's voice. These symptoms developed in one day and progressed. In addition, she had cough and rhinorrhea.

At the ED, she had a fever (38.1 °C) with slight leukocytosis (white blood cell count: 11,000/μL) and her vital signs were stable. A cerebrospinal fluid (CSF) study and neurological examination was normal. She was admitted and was administered risperidone (1 mg/day) to control her psychotic symptoms.

After admission, the patient displayed poor attention, and stereotypical behavior with intact orientation on the second day (D2). Her condition progressed rapidly with greater fluctuation on D3. She displayed self-absorption intertwined with intermittent psychomotor agitation and purposeless behavior. She could not recognize the doctor who had visited her the day before. The electroencephalography (EEG), single photon emission CT (SPECT) scan, autoimmune profile and thyroid function results were normal. Viral culture and serology and herpes simplex virus nucleic acid examination in the CSF resulted in negative findings. Organic catatonia was suspected and risperidone was discontinued on D4. The patient developed oro-lingual dyskinesia and tachycardia on D5. A fever emerged on D7 and aspiration pneumonia was favored. The patient was taken home against medical advice on D8. She returned to our hospital on D10 with consciousness disturbance and respiratory failure, resulting in intubation. Two episodes of clonic seizure occurred on D11. Repeat of the CSF examination showed negative findings. The patient was taken to another hospital on D11.

Midazolam and valproic acid were administered for suspected seizure. An EEG on D11 showed widespread alpha-beta activities without re-activity to acoustic or pain stimuli. Pulse therapy with methylprednisolone, during D13 to D15 (1 g/day), failed to have any effect. An EEG on D16 showed a disorganized slow background superimposed with widespread beta activity. A brain MRI with contrast showed no significant findings. A D15 sample of CSF was confirmed to be positive for the NMDAR antibody by Dr Josep Dalmau's laboratory.[4] Abdominal/pelvic sonography and an abdominal CT were both negative. Intravenous immunoglobulin (IVIG) was administered during D17–D20 (1 g/kg per day for the first day, 0.5 g/kg per day for the second and third days; 2 g/kg in total). The patient exhibited greater awareness to stimuli. She was extubated smoothly on D27. Gradually, her attention and activity recovered, and she was able to talk. She resumed oral feeding on D33 and was mobile in a wheelchair on D36. After discharge on D38, she returned to the outpatient department for follow-up on D42, and presented with clear consciousness. She experienced satisfactory sleep and was able to eat by herself. She still had lower limb weakness and slow speech. She was subsequently lost to follow-up.

3. Discussion

Anti-NMDAR encephalitis predominantly affects young females with an ovarian teratoma.[2] However, the disease is recognized increasingly in males, children, and patients without a detectable tumor (non-paraneoplastic).[3,5] In one series of 44 patients, 30% were male, 23% were children, and 20% were patients with paraneoplastic disease.[6] Neoplasm is less frequently encountered in children.[7]

This condition usually evolves through several stages: flu-like prodromal symptoms, a psychotic stage, unresponsiveness with hypoventilation, autonomic instability and dyskinesia, and eventually death or recovery.[2,4] The unresponsive stage is accompanied by catatonia-like symptoms,[2] and dyskinesia most often begins in the face and mouth.[2]

The brain MRI is often normal, but there may be abnormalities in the medial temporal lobe, cerebellum, basal ganglion, or brain stem.[4–6] The results of positron emission tomography are limited.[8] Most CSF studies show lymphocytic pleocytosis and oligoclonal bands.[4] Most EEG show slow activity without epileptic discharges.[5] Diagnosis has been facilitated by the detection of antibodies to NMDAR in the serum or CSF.[2]

Anti-NMDAR encephalitis dramatically improves following tumor resection and immunotherapy, including corticosteroid, IVIG or plasma exchange, cyclophosphamide, rituximab, and azathioprine.[3,4] Long-term maintenance immune-suppression is suggested for reduction of antibody titres intensively.[6] Symptoms may relapse in patients with no tumors or recurrent tumors.[4,5] Relapses in up to 10 of 35 patients with non-paraneoplastic anti-NMDAR encephalitis had been reported.[6] Interestingly, patients with non-paraneoplastic NMDAR encephalitis have a poorer response to immunotherapy than patients with paraneoplastic encephalitis.[4,6]

The immunopathological findings of anti-NMDAR encephalitis are increased reactive microglia staining with anti-CD68 antibody and deposits of immunoglobulin G, predominantly involving the hippocampus, basal forebrain, basal ganglion and cervical spinal cord.[4,5,9] The findings are different from the extensive infiltrates of cytotoxic T-cells in most patients with non-anti-NMDAR paraneoplastic encephalitis.[9] The antibodies have a selective and reversible effect on NMDAR[4] and the antibody titres are correlated with clinical severity.[4,5,9] These findings may explain the better prognosis for anti-NMDAR encephalitis.

Anti-NMDAR encephalitis is usually misdiagnosed as a psychiatric disorder initially.[2] Anti-NMDAR encephalitis is also a frequent disorder among young patients in intensive care units who have neuropsychiatric symptoms.[10–12] Early identification and intervention can shorten the duration of intensive care admission and ventilation, improve the outcome, and protect against relapse.[2,6]

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A primary orbital hydatid cyst

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ABSTRACT

Echinococcosis, caused by the tapeworm *Echinococcus granulosus*, is an endemic zoonosis in which humans act as accidental intermediate hosts. Orbital hydatid cysts comprise 1% to 2% of all hydatid lesions. We describe a 10-year-old boy with an orbital hydatid cyst. The orbital cyst was removed totally by frontal craniotomy and orbitotomy. It should be noted that unilateral painless proptosis in patients from countries endemic for echinococcosis could be caused by an orbital hydatid cyst.

1. Introduction

Echinococcosis, caused by *Echinococcus granulosus*, is a zoonosis in which humans act as accidental intermediate hosts. Infestation by larvae of the tapeworm *Echinococcus granulosus* causes a hydatid cyst. The oncospheres that hatch from ingested eggs penetrate the intestine and can then be carried, via the portal and systemic circulations, to almost any organ of the body, where they may develop into hydatid cysts.[1]

Echinococcosis is endemic in some countries. The most common sites of infestation in humans are the liver (60–70%), lungs (20%), and less frequently the heart, spleen, kidney, brain, thyroid, bones, and muscles.[1,2] Orbital hydatid cysts cause 1% to 2% of all hydatid lesions.[2] The orbital hydatid cyst is generally unilateral.[2] Patients are mostly children or young adults.[3] Orbital hydatid cysts usually present in the form of slowly progressing painless unilateral proptosis.

2. Case report

A 10-year-old boy was admitted with right painless proptosis. The eyeball was non-reducible and non-pulsatile. The pupils were equal and reacted normally to light. Ocular movements were restricted laterally and superiorly. Fundoscopic examination revealed disc swelling and engorged retinal veins. The visual field examination showed enlargement of the blind spot. The left eye was normal. The general physical findings were normal. Abdominal and chest CT scans showed no pathology. Routine laboratory tests were normal. A serological test for echinococcus was negative. The lesion on MRI appeared as a hypointense cystic space with well-defined borders, with a thin homogenous wall surrounded by a hyperintense wall. The orbital MRI showed a well-defined, intraconal inferolaterally localized 22 mm × 23 mm × 24 mm cystic lesion, a superiorly displaced optic nerve and rim enhancement on contrast injection (Fig. 1). The orbital cyst wall was removed totally by frontal craniotomy and orbitotomy (Fig. 2). The cyst wall was accidentally ruptured during the resection. External capsule of the cyst was dissected from the intraorbital structures, and the cyst was resected totally (Fig. 3). The surgical area was irrigated with hypertonic saline. After surgical treatment, the patient had no ocular movement abnormalities, and his proptosis improved. The patient was managed postoperatively with oral albendazole (15 mg/kg twice per day for three months). There was no clinical evidence of recurrent disease at the 12-month follow-up.

3. Discussion

An orbital hydatid cyst is rare. Echinococcosis is endemic to Africa, the Middle East, the Mediterranean region, Australia, New Zealand and South America.[4,5] Our patient was from a rural area, and had come into contact with sheep, cattle, and dogs. The most common presenting clinical symptoms and signs are non-pulsatile, non-tender proptosis, visual disturbances, disc swelling, diplopia, chemosis, eyelid edema, and conjunctivitis.[6] The hydatid cyst grows to 1 cm to 5 cm in diameter and unilateral proptosis usually ranges in duration from three months to two years.[7] In endemic areas, orbital hydatid cysts represent 5% to 20% of all orbital tumors.[5] Other orbital cystic lesions are respiratory epithelial cyst, dermoid cyst, epidermoid cyst, teratoma, haematic cyst, abscess, mucocele, and encephalocele.[1,8] The hydatid cyst that develops in or near the eye usually forms in the orbit, the muscle cone being the most frequent location, followed by the superomedial and superolateral orbit and then, as an exception, within the medial rectus muscle, subretinal space, anterior chamber or vitreous cavity.[1,8,9] In our patient, the cyst was located inferolaterally, which is rare.[2,10] On MRI the cysts appear as a low intensity signal on T1-weighted images and high-intensity signal on T2-weighted images.[8] The cysts show peripheral rim enhancement in their fibrous capsule.[8] CT scans and MRI are very important for diagnosis.

The pre-operative laboratory tests in our patient were normal. After the initial diagnosis, it is important for albendazole treatment to be applied 14 days to 28 days before surgery if possible.[3] In systemic hydatidosis, serology is generally positive. However, for cerebral and intracranial hydatid cyst tests are almost always negative.[11–13] The Cassoni intradermal test, counter-immunoelectrophoresis, double-diffusion tests and indirect hemagglutination

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