LETTERS

Testicular teratoma and anti-N-methyl-D-aspartate receptor-associated encephalitis

We report a patient with a testicular teratoma and seminoma, who developed treatment-responsive encephalitis associated with antibodies to NMDA receptor, but not antibodies to Ma2 protein.

A 30-year-old male was admitted to hospital with a 1-week history of personality changes, confusion, agitation and recurrent generalised tonic-clonic seizures. His past medical history was unremarkable, except for the presence of generalised fatigue and sore throat a few days before symptom onset. On physical examination, the only pathological finding was bilateral testicular enlargement. He was agitated and disoriented to time, place and person; his speech was incoherent, and he had persecutory and erotic delusions. The rest of the neurological examination was normal. The initial laboratory studies, including complete blood count, biochemistry, EEG and brain MRI, were normal. The CSF examination was significant for an elevated protein concentration (113 mg/dl) with normal glucose content and mild leukocytosis (25 cells/μl); bacterial and viral studies, including PCR for herpes simplex virus, were negative. Testicular ultrasound revealed the presence of a left testicular mass and right testicular torsion. Computerised tomography of the chest, abdomen and pelvis demonstrated the presence of a retroperitoneal lesion, which was suggestive of metastasis. These findings led us to consider the diagnosis of paraneoplastic encephalitis. Accordingly, CSF samples were preserved for serological studies and right inguinal orchiectomy and left partial orchiectomy were performed urgently. Pathological examination disclosed a pure seminoma in the left testis. The tumour on the right side was a mixed germ-cell tumour composed of seminoma and teratoma with small foci of embryonal carcinoma. Although sparse, neural tissue was present in the teratoma and this was confirmed by positive immunohistochemical staining for MAP2, a marker of neuronal dendritic processes (fig 1A). While waiting for the results of immunological studies, the patient was treated with intravenous methylprednisolone (1 g/day, for 7 days), and then with intravenous immunoglobulin (30 g/day for 5 days). No clinical response was achieved and he continued to deteriorate. Despite antiepileptic treatment, the patient developed a secondary generalised tonic-clonic seizure and frequent episodes of autonomic instability with brady-tachycardia, severe diaphoresis and apnoea. Echolalia, lingual dyskinesias, dystonic jaw closing, and repetitive dystonic and choreiform movements of feet and fingers were noted. Eventually, he became unresponsive, with generalised rigidity and catatonic posturing. EEG revealed voltage suppression and generalised slowness at this stage. An ictal recording revealed propagation of epileptic activity from the right parieto-occipital region. One month after admission, a repeat MRI showed a subtle increase of FLAIR signal in the amygdala and hippocampi, more prominent on the right side (fig 1B). Absence of signal abnormality on initial MRI might be due to either development of the signal changes in the time period between the two scans or inherent sensitivity of the FLAIR to subtle signal abnormalities. Single voxel (^{1}H) MR spectroscopy study of a 1.5 cm^3 cube from the right amygdala and anterior aspect of hippocampus corresponding to the area of increased signal on the FLAIR images showed a mild decrease in NAA/Cr and an increase in Cho/Cr (NAA/Cr: 0.94; Cho/Cr: 0.91). Further CSF studies revealed the presence of antibodies to NR1/NR2 heteromers of the NMDA receptor; antibodies to Ma1/2 and voltage-gated potassium channels were not found. Chemotherapy with bleomycin, etoposide and cisplatin was started. After the second course of chemotherapy, the patient started to recover gradually, and in 6 weeks the recovery was complete without neurological deficits. Mini-mental status examination score was 29/30. Neuropsychological assessment—including reciting months forward and backwards, digit span test, clock drawing, memory assessed by enhanced cued recall, trail A and B and semantic fluency for animal category—were normal, except for a mild decrease in verbal fluency. After recovery, the retroperitoneal lesion was removed. Pathological examination revealed metastatic teratoma without other germ-cell components; however, the stroma showed somatic-type malignant transformation in the form of high-grade sarcoma. Surgical margins of the resection were clear.

DISCUSSION

These findings expand our current understanding of autoimmune encephalitis in several aspects. To our knowledge, this is the first case of teratoma-related anti-NMDA receptor encephalitis in a man. Furthermore, our patient had a seminoma and retroperitoneal metastasis. Similar to other cases of anti-NMDAR encephalitis, a dramatic clinical recovery occurred despite the severity of the neurological symptoms. In our patient, this recovery was probably related to an aggressive tumour treatment that included surgery and chemotherapy.

This case shares typical clinical features of paraneoplastic anti-NMDA receptor encephalitis associated with ovarian teratoma, including occurrence at a young age, seizures, and cognitive and psychiatric symptoms accompanied by sequential development of predictable neurological features.[1] These included autonomic and respiratory instability and distinctive signs of extrapyramidal involvement, along with symptoms of limbic dysfunction. Because of the rapid clinical deterioration and lack of response to immunotherapy, anti-Ma1/2-associated encephalitis related to seminoma was initially suspected.[2 3] However, the detection of antibodies to NMDA receptor and not to Ma1/2 antigens was not surprising, considering the indicated characteristic clinical features, subtle MRI findings and almost full neurological recovery. As previously noted, our patient also had flu-like

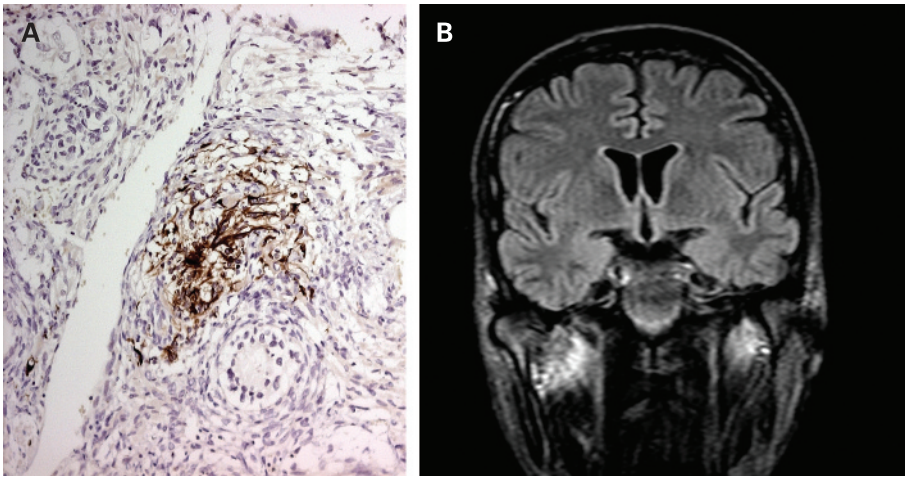

Figure 1 Tumour and brain MRI of the patient. (A) A micrograph of the patient's teratoma showing a small focus of neurons (dark brown) with intense expression of microtubule-associated protein 2 (MAP2), a specific marker of neuronal dendritic processes (Immunohistochemistry, anti-MAP2 antibody, ABC × 200). (B) Coronal FLAIR (TR/TE/TI; 8400/100/2100 ms) image shows subtle increased signal intensities on both amygdala.

prodromal symptoms, suggesting that an infectious process might contribute to triggering the immune response.[4] The serological findings of our case are similar to the previous reports of encephalitis associated with ovarian teratoma, with specific antibodies against NR1/NR2 subunits of NMDA receptor. As emphasised by Tüzün and Dalmau,[4] the prognosis of limbic encephalitis differs between disorders associated with antibodies to intracellular antigens (eg, anti-Ma1/2) and those with antibodies to cell membrane antigens (eg, anti-NMDAR antibodies), with the latter having a better prognosis. The complete recovery of our patient supports this observation. In our case, however, recovery did not appear to be related to immunotherapy, but rather to resection of the primary tumour and chemotherapy, despite the presence of a retroperitoneal metastasis. A spontaneous recovery can be argued for, as has been reported in a few patients with anti-NMDA receptor encephalitis.[5] However, our patient was different from such cases in which improvement occurred in several months, as our patient's improvement was noted early after the chemotherapy was started, resulting in a near full recovery in 6 weeks.

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Dyspnoea due to vocal fold abduction paresis in anti-MuSK myasthenia gravis

CASE REPORT

A 24-year-old female student who had inspiratory stridor and exertional dyspnoea for 2 years was seen in our neurology and otolaryngology outpatient department. The dyspnoea disabled her in walking stairs and stridor occurred after physical exercise, such as walking stairs or talking. In addition, in the past 2 years, she had suffered from recurrent episodes of diplopia, which intensified in the evening; this had been diagnosed as decompensated oesotropia. She also complained of difficulty in swallowing, but had no problems chewing. On physical examination, rhinolalia aperta, right-sided ptosis, weakness of neck flexors and a myopathic face were found. She was submitted to respiratory function tests. Her spirometry showed no decrease in vital capacity (110%). A flow volume loop (FVL) after physical exercise showed an inspiratory plateau, indicating an inspiratory airway obstruction. On laryngoscopy, a bilateral abduction paresis of the vocal folds was seen with a maximum abduction angle of 15 degrees (normally 30–70 degrees) between the vocal folds (fig 1A). Because of the clinical signs, myasthenia gravis was suspected. Anti-acetylcholine receptor antibodies (anti-Ach-R-abs) were negative and no typical decrement on low-frequency repetitive nerve stimulation was shown. A neostigmine test resulted in adverse effects, making it impossible to observe any positive results. Anti-muscle-specific kinase antibodies (anti-MuSK-abs) were present, which led to the diagnosis of anti-MuSK-ab-positive myasthenia gravis. She was first treated with pyridostigmine for 6 weeks at a maximum of 80 mg a day, which did not improve her complaints, but gave significant side effects. Treatment with prednisone 25 mg daily was started, after which her complaints and symptoms, including the vocal fold paresis (fig 1B), subsided.

DISCUSSION

Vocal fold abduction paresis (VFAP) can result from many different conditions and, by enhancing the airway resistance, can induce an inspiratory stridor.[1] The VFAP is thought to produce an obstruction by weakness of the vocal cord abductors (*posterior cricoarytenoid muscle*). VFAP is, apart from laryngeal electromyography, best detected by laryngeal endoscopy or the evaluation of a FVL, but not spirometry. The VFAP becomes visible as an inspiratory plateau in the FVL, which is indicative of an inspiratory airway obstruction.

VFAP is believed to be a rare manifestation of myasthenia gravis. In a retrospective study consisting of 1520 Chinese patients investigating dysphonia as the primary manifestation of myasthenia gravis, 7 patients were found to suffer from laryngeal muscle involvement.[2]

One prior report of anti-MuSK myasthenia gravis and VFAP was found in the literature.[3] In the particular case report of the anti-MuSK patient with myasthenia gravis, the patient had complaints of stridor and dyspnea for 3 months before the diagnosis of VFAP was made and pulmonary function tests showed a reduction in ventilatory muscle strength; however, there was no report of a FVL by the authors. The diagnosis of VFAP was made using fibreoptic laryngoscopy. The diagnosis of myasthenia gravis was delayed by a negative edrophonium test and was only made after repetitive nerve stimulation tests and a positive anti-MuSK-ab test. The patient underwent tracheostomy. Almost 4 months after the diagnosis of VFAP and tracheostomy, prednisone therapy was started. The patient recovered only partially after prednisone therapy and still required tracheostomy 6 months after initiation of the therapy.

In a study on the laryngeal manifestations of 40 patients with myasthenia gravis, anti-Ach-R-abs were measured in 33 patients;

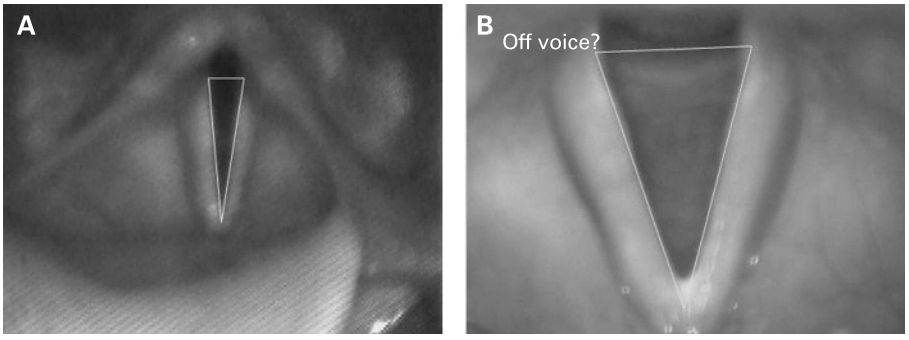

Figure 1 Stroboscopic laryngoscopic pictures of the vocal fold at maximal abduction. (A) Before prednisone treatment, showing a maximum abduction angle of 15 degrees between the vocal folds. (B) After prednisone treatment, showing a maximum abduction angle of 33 degrees between the vocal folds.

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