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Case report

Acute behavioural change in a young woman evolving towards cerebellar syndrome

G. Naeije*, Q. de Hemptinne, C. Depondt, M. Pandolfo, B. Legros

Department of Neurology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

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ABSTRACT

Symptomatic paraneoplastic neurological syndromes are rare manifestations of cancers. Recently, a new type of encephalitis associated with antibodies against NMDA-glutamate receptors (A-NMDAR) was defined. The patients, usually young women, present with acute onset of psychiatric symptoms and decreased consciousness. We describe the case of a patient who presented with acute onset of delirium alternating with sub-comatose state. Blood analyses were within normal range. Lumbar puncture showed lymphocytic pleiocytosis. Brain gadolinium injected MRI, brain and full body PET scans were normal. Investigations led to suspect a paraneoplastic syndrome and a right ovarian teratoma and A-NMDAR were found and the teratoma removed. The remaining sequellae included a cerebellar syndrome seldom described before. As cerebellar and cortical neurons share the same excitatory pathway through NMDA-glutamate receptors, the cerebellar function impairment observed in our patient could be explained by a disabling action on glutamate NMDAR by the A-NMDAR.

1. Introduction

Symptomatic paraneoplastic neurological syndromes are rare manifestations of cancers. Recently, a new type of encephalitis associated with antibodies against NMDA-glutamate receptors (A-NMDAR) was defined. The patients, usually young women, present with acute onset of psychiatric symptoms and decreased consciousness. Abnormal movement and seizures are often found but a cerebellar syndrome has been exceptionally described. We report a case of a young woman with A-NMDAR encephalitis evolving towards cerebellar syndrome.

2. Case report

We report the case of a 29-year-old woman who presented with acute onset of delirium alternating with sub-comatose state. Ten days before her admission, the patient went nightclubbing and returned at dawn. She was then reported as "out of character" and behaving like drunk, although she was sober. The following week, behavioural alterations exacerbated. At work, she could not concentrate. Concerned, she asked to be driven to the emergency room (ER) of another hospital. In the car, she began to shout and have uncontrolled movements. Afterwards, she alternated between a lethargic, unreactive state and extreme agitation. She had no past medical history, took no medication and had not travelled recently. Family and friends reported she had never used drugs. Physical examination was there described as normal. The ER blood analyses were within normal range, including a complete blood count, electrolytes, kidney, liver and inflammatory parameters and urinary toxicology screening. A brain computed tomography (CT) scan was normal. The cerebrospinal fluid (CSF) analysis revealed 24 white blood cells (90 percent lymphocytes) per milliliter (normal range < 5/mL), with normal chemistries. The patient was empirically treated with ceftriaxone, ampicillin and acyclovir. As the direct examination and the culture of the CSF resulted negative, ceftriaxone and ampicillin were stopped. Her condition continued to worsen and 4 days after the onset of the delirium, the patient was transferred to our institution.

On admission, we were confronted with a deeply agitated woman whose physical examination was unremarkable. She was afebrile. The neurological examination was limited due to lack of collaboration. She seldom answered simple questions, but sometimes uttered an adequate sentence and then resumed to shouting incoherent sounds. There was no sign of meningeal irritation, the pupils were symmetric and reactive to light, there was no apparent oculomotor or facial palsy. She moved her four limbs against resistance. Deep tendon reflexes were present and symmetric. The only positive neurological sign was a right plantar reflex in extension. Since there had been no improvement with antiviral and antibiotic treatment, a trial with 1000 mg of methylprednisolone per day during 5 days was undertaken. There was

* Corresponding author at: Department of Neurology, Erasme Hospital, 808 Route de Lennik, 1070 Brussels, Belgium. Tel.: +32 477542862; fax: +32 2 555 3942.
E-mail address: gillesnaeije@yahoo.com (G. Naeije).

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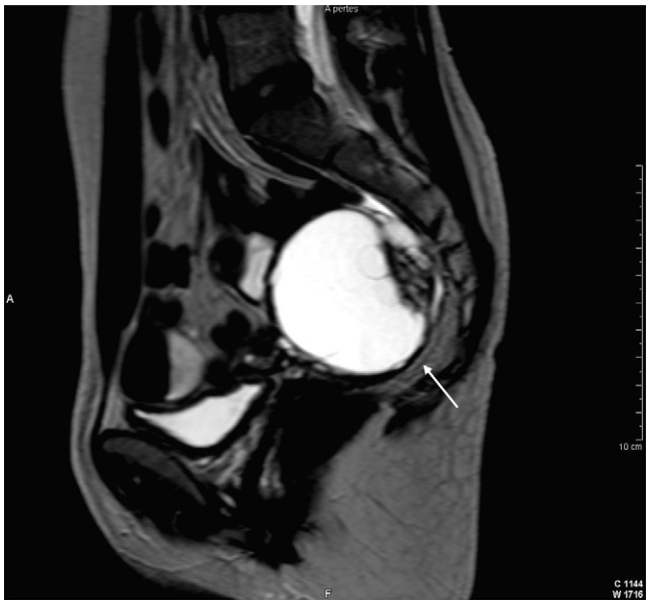

Fig. 1. T2 weighted pelvic MRI revealing a 5 cm × 3 cm × 2 cm heterogenous mass in the right ovary (white arrow). Anatomopathologic examination disclosed a teratoma.

absolutely no change in her clinical state. Blood analysis showed no inflammatory syndrome: white blood cells were masured at 8000/mm^3 (normal range < 10,000/mm^3), C reactive protein at 9.4 mg/L (normal range < 10 mg/L), erythrocyte sedimentation rate at 4 mm/h (normal range < 20 mm/h), anti-nuclear antibodies were negative, anti-neutrophilic cytoplasmic antibodies were positive at 1:40 dilution without specificity against proteinase 3 or myeloperoxydase. A lumbar puncture was reiterated and showed 10 lymphocytes per milliliter. Proteins and lactate were normal and no oligoclonal bands were detected. We performed a broad serological screening including Borrelia burgdorferi, toxoplasma, syphilis, arboviruses, rabies, enteroviruses, herpes simplex, herpes zoster: all were negative. Human immunodeficiency virus (HIV) serology and polymerase chain reaction (PCR) were negative on both blood and CSF. Analysis of haeme metabolites and amino acids on urine ruled out porphyria and urea metabolism disorders. A 24 h video-electroencephalogram showed rare sharp waves over the left temporal region. A brain MRI with gadolinium injection, a trans-cranial Doppler and a fundoscopic examination were normal. A paraneoplastic syndrome was then suspected. Hu, ri and antiganglioside antibodies were negative. A whole body positron-emission tomography scan (PET) was normal. Brain PET disclosed a bilateral posterior hypometabolism. This patient's clinical course resembled several cases of encephalitis associated with ovarian teratoma and A-NMDAR, prompting us to perform a pelvic MRI that revealed a 5 cm × 2 cm × 3 cm ovarian teratoma (Fig. 1). We subsequently tested for the presence of A-NMDAR which were positive.

Five weeks after the onset of symptoms, the patient started to wake up and communicate for increasing periods of time. The ovarian teratoma was surgically removed and the patient continued to improve. Fourteen weeks after the onset of symptoms, the remaining sequelae were severe orthostatic hypotension without any increase of heart rate, disinhibition and a cerebellar syndrome. Neurological examination disclosed cerebellar, pyramidal and frontal abnormalities. There was mental slowing, scanning speech, square-waves jerks on ocular pursuit, bilateral hypermetria on the finger-to-nose test and impaired heel-to-shin test. Rapid alternating movements were impossible. The plantar response was in extension on the right side. Gait was ataxic and tandem gait was impossible. The tonus, muscle strength, and sensation were normal.

Table 1

Toxicologic
Phenylcycline, LSD, cocaine, amphetamines, cannabis, . . .
Metabolic
Acute porphyria
Urea cycle disorder
Endocrine psychosis
Electrolyte imbalance
Infectious
Viral: HIV, JC virus, HSV1, HSV2, VZV, HHV6, CMV, EBV, rabies, . . .
Bacterial: tuberculosis, Listeria
Vector transmitted: borreliosis, arbovirosis, trypanosomiasis, malaria
Fungal and parasitic: cryptoccocosis, toxoplasmosis
Systemic autoimmune or vasculitic
SLE, Sjögren's syndrome
Primary angiitis of the central nervous system
Epileptic
Temporal lobe epilepsy
Neoplastic
CNS lymphoma
Primary brain tumour
Metastatic disease
Paraneoplastic
Limbic encephalitis
Encephalitis with ovarian teratoma and anti-NMDAR
Encephalitis with VGKC-A

HIV = human immunodeficiency virus, HSV = herpes simplex virus, VZV = varicella zoster virus, HHV = human herpes virus, CMV = cytomegalovirus, EBV = Epstein Barr virus, SLE = systemic lupus erythematous, VGKC-A = voltage-gated potassium channel antibodies.

3. Discussion

The differential diagnosis of organic psychosis is wide and summarized in Table 1. In this case, systematic exclusion of each diagnostic entity made us suspect a paraneoplastic syndrome. The clinical pattern of our patient and the absence of specific antibodies (anti-Hu, anti-Ma2, . . .) rules out paraneoplastic limbic encephalitis [1]. Hallucinatory behaviour and cognitive impairment hint towards encephalitis with anti-voltage-gated potassium channel antibodies but the other features associated: hyponatremia, autonomic hyperactivation and antibodies against voltage-gated potassium channels were missing [2]. Prominent psychiatric symptoms are also the hallmark of the recently described encephalitis associated with A-NMDAR and ovarian teratoma. Further imaging led us to discover an ovarian teratoma and the diagnostic was confirmed by the discovery of A-NMDAR in the serum.

Encephalitis associated with A-NMDAR was recently defined in a series of 100 adult patients and in a smaller series of 32 children. In adults, the median age is 23 years, 90 percent of patients are women, all present with psychiatric symptoms and 88 percent with decreased consciousness. Dysautonomia, seizures, dyskinesias and hypoventilation occur in more than two-third the cases. Only one case associating ataxia with opsoclonus-myoclonus and the present case report had cerebellar features [4]. CSF shows inflammatory alterations, flair or T2 weighted brain MRI signal shows hyperintensities in the temporal lobes and PET shows hypermetabolism in one or both temporal lobes. PET anomalies can precede the signal anomalies on MRI and about half the patients have normal imaging [4,6]. An ovarian teratoma is found in 60 percent of the cases. In women, ovarian teratoma must be looked for, since the removal of the teratoma induces a fall in A-NMDAR titre [5] and is associated with a better outcome and less relapses. 17 months after the onset, half the patients remain with frontal lobe dysfunction like behavioural dysinhibition, attention and planification disorders. In children, a tumour is less likely to be found and autonomic distur-

bances are less severe but more frequent than in adults [7]. The sequels are severe in 25 percent of adult cases. In our case, after 3 months, there was no obvious improvement but recoveries have been known to happen even after several months.

NMDA receptors (NMDAR) play a key role in neuronal excitatory pathways and plasticity throughout the central nervous system. Pharmacological antagonists of the glutamate NMDAR can cause symptoms of psychotic behaviour in human [8]. The prominent behavioural disorders in patients suffering from encephalitis associated with A-NMDAR led to suspect a pathogenic and antagonistic effect of the antibodies on the NMDA receptors. This hypothesis is supported by studies showing that A-NMDAR binds the NR1 subunit of the NMDAR and that application of A-NMDAR to culture of hippocampal neurons decreased postsynaptic NMDA clusters. Furthermore, clinical neurological improvement correlates with decreasing antibodies titre [6]. Similar impairement of the NMDAR in the nucleus tractus solitari could explain autonomic features like orthostatic hypotension [9]. As cerebellar and cortical neurons share the same excitatory pathway through NMDA-glutamate receptors an alteration of cerebellar function by A-NMDAR is expected [10]. The cerebellum could be less sensitive to A-NMDAR than other brain structures making its impairment an atypical manifestation of this autoimmune disorder. Encephalitis associated with A-NMDAR is a recently described disease in which A-NMDAR have been demonstrated to have a functional effect. The NMDAR are widely expressed in the central nervous system making nucleus tractus solitari, cortical and cerebellar neurons potential targets for alteration by A-NMDAR.

Conflict of interest

The authors have no conflict of interest.

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