Clinical case

Lethal acute demyelinization with encephalo-myelitis as a complication of cured Cushing’s disease

Encéphalopathie aiguë démyélinisante d’évolution fatale au décours d’une guérison de maladie de Cushing


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Available online 17 September 2010

Résumé

La maladie de Cushing est habituellement associée à une surmortalité, en particulier cardiovasculaire. Après guérison, la normalisation de la sécrétion glucocorticoïde peut s’associer à l’apparition ou à l’exacerbation de maladies auto-immunes ou inflammatoires. Nous rapportons pour la première fois l’observation d’une femme de 34 ans qui a développé une encéphalopathie aiguë démyélinisante au décours de la guérison d’une maladie de Cushing, dont la présentation clinique atypique sur un mode psychiatrique associée à la suppression de la sécrétion glucocorticoïde endogène a précipité l’évolution fatale.

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Mots clés : ADEM ; Encéphalopathie ; Démynélinisation ; Hypercortisolisme ; Maladie de Cushing

Abstract

Cushing’s disease is usually associated with higher mortality rate, especially from cardiovascular causes. Development or exacerbation of autoimmune or inflammatory diseases is known to occur in patients with hypercortisolism after cure. We report for the first time a 34-year old woman who presented with severe psychiatric background, who developed four months after the surgical cure of Cushing’s disease an acute disseminated encephalomyelitis (ADEM) presenting initially as a psychiatric illness. We hypothesize that the recent correction of hypercortisolism triggered ADEM and that the atypical presentation, responsible for diagnosis delay, led to the death of this patient.

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Keywords: Acute disseminated encephalomyelitis; Encephalitis; Demyelinisation; Hypercortisolism; Cushing’s disease

1. Introduction

Cushing’s disease is usually associated with higher mortality rate, especially from infectious and cardiovascular causes, such as high blood pressure and its complications, or thrombo-embolic affections. Diagnosis can be difficult as psychiatric symptoms are not rare and can be extremely severe. After cure,
glucocorticoids secretion normalization can be associated with onset or exacerbation of auto-immune or inflammatory disorders [1]. We report here an observation of Cushing’s disease, which was complicated by a lethal acute disseminated encephalomyelitis (ADEM) occurring a few weeks after its cure.

2. Case report

A 34-year-old woman with a history of psychosis (many hospitalizations during her adolescence with repeated suicide attempts) presented to our endocrine ward with android obesity (weight 96 kg, height 154 cm; body mass index 40.4 kg/m²), dark stretch marks, type 2 diabetes mellitus and severe depression. She was therefore diagnosed with Cushing’s disease. She benefited from a trans-sphenoidal neurosurgery a few weeks after diagnosis and a pituitary macro-adenoma of 15 mm developed at the left side of the anterior gland was removed. Immuno-histological analysis confirmed the diagnosis of Cushing’s disease, as cells stained for ACTH only, with a proliferation index (Mib1) lower than 1%. There was no post-operative complication and the patient was considered cured based on results of dexamethasone suppression and desmopressin (ddA VP) tests. She had however an isolated gonadotrophic insufficiency, which was not treated (Table 1). Early evolution was favorable: she lost 21 kg and her glycemic profile normalized allowing us to stop anti-diabetic drugs. However, psychiatric state remained unchanged.

Four months after neurosurgical intervention, she was hospitalized because of incoercible vomiting while she was coming back from a one-month trip to South Algeria. Vomiting was isolated without digestive, neurological or other signs, except for a febricula (37.8 °C). Biological assessment only showed a hypokaliemia (2.9 mmol/l). Gastroscopy was performed showing a pangastritis without *Helicobacter pylori* infection. Thus, the patient was treated by proton pomp inhibitor (esomeprazole) twice a day during seven days, then once a day. Two weeks later, she presented an acute confusion then a mutism. Hystera conversion was initially suggested considering her psychiatric background. However, she developed on a fourth day a low degree fever (37.9 °C) associated with areflexic tetraparesis. A lumbar puncture was performed and cerebrospinal fluid examination only showed an elevation of protein level (1.51 g/l) without any pathogen. Biological assessment was normal except for a moderately increased C-reactive protein (8.3 mg/l; N < 3 mg/l); no vitamin deficiency was noticed. The patient had no focal cortical signs, cranial nerve abnormality.
Brain magnetic resonance imaging (MRI) performed three months after surgical resection of pituitary adenoma and just one month before patient’s death without any pre-existing demyelination signal. A. Axial T1-weighted image. B. Sagittal FLAIR-T2-weighted image. C. Axial T1-weighted image with focus on pituitary showing no tumoral residue. D. Axial T2-weighted image with focus on pituitary.


(such as ophthalmplegia), nor sensory deficit; all deep tendon reflexes were abolished and Babinski’s sign was absent. Cranial CT-scan was strictly normal, as well as electroencephalogram. Brain magnetic resonance imaging (MRI) could not be performed considering the very fast evolution, which led to the death of the patient two days later. However, brain MRI had been performed one month earlier and was completely normal (Fig. 1). Infectious (herpes, rabies) or inflammatory encephalomyeloneuropathy (such as a subacute multiple sclerosis) was thus suspected. The presence of HSV 1 and 2, VZV, CMV and Bordetella pertussis and parapertussis in cerebrospinal fluid was ruled out by polymerase chain reaction (PCR). Lack of brain MRI led us to perform an autopsy. No abnormality was noticed during macroscopic examination of meninges and brain.

Histopathological findings were characterized by multifocal lesions of vascularitis in brainstem, cerebellum and thalamus, especially around the ependyma (Fig. 2). These lesions combined oedema, endothelial swelling with micro-haemorrhages and unspecific perivascular infiltration of veins and capillaries with CD3+ CD8+ T cells (Fig. 3). Specific Luxol fast blue staining demonstrated demyelination in the same perivascular areas, without confluences; axons were preserved as shown by neurofilament staining. Specific colorations (Gram, Grocott, Ziehl and Warthin Starry) failed to detect any pathogen, and rabies virus was ruled out by several assays (immunofluorescence, viral isolation and ELISA detection). No viral cytopathogenic effect was detected. These histopathological features suggested in fact an unspecific CD3+ CD8+ lymphocytic rhombencephalitis with

Fig. 2. Microscopic examination of mesencephali. A. Diffuse infiltration with macrophages and lymphocytes (HES × 200). B. Positive immunostaining for anti-CD3 (×400). C. Negative immunostaining for anti-CD20 (×400).

demyelination. Bickerstaff encephalitis (subgroup of ADEM with demyelination confined to brainstem) was excluded as antineuronal antibodies (especially anti-Hu and anti-ganglioside Gq1b antibodies) were not detected in cerebrospinal fluid and in serum sampled before death. We conclude to the diagnosis of acute inflammatory encephalitis with demyelination, or acute disseminated encephalo-myelitis (ADEM).

3. Discussion

Acute disseminated encephalo-myelitis is a rare disorder with an estimated incidence of 0.4–0.8 per 100,000 population per year [2]. Young and adolescent children are most commonly affected with a median age at diagnosis of 6.5 years [3]. Precise pathogenetic concepts are still unknown but experimental data indicate that both primary autoimmune responses and immune responses secondary to an infection may contribute to encephalitis and subsequent demyelination. Specific T cells are responsible for such immune responses and determine infiltration of perivascular areas and acute or subacute demyelination of white matter [4,5], which could result in very serious complications. In about 70 to 75% of all cases, the clinical onset of disease is preceded, with an average latency of four days to five weeks, by viral or bacterial infections (such as chickenpox, mumps, measles, EBV, HSV or CMV) or by a vaccination, especially measles vaccination (post-immunization encephalomyelitis). However, it is of note that the incidence of a measles vaccination-associated ADEM is about 10 to 20 per 100,000 vaccinated patients and thus considerably lower than the incidence of ADEM developed after a wild-type measles encephalitis (100 per 100,000 infected individuals) [3].

Neurological signs and symptoms develop subacutely over a period of days and lead to hospitalization within a week. No neurological sign is specific or pathognomonic but in adult cases headaches with or without fever, motor or sensory defect, ataxia, cognitive defect or even lethargy are most commonly reported. In general, the clinical presentation of ADEM is very heterogeneous with a combination of altered consciousness or behavior and multifocal neurological deficits, allowing to distinguish ADEM from multiple sclerosis, its most important differential diagnosis [4]. Psychiatric features are unusual and mostly reported in children before 10 years of age [6]; they could explain a diagnosis delay, which is responsible for severe injuries and unfavorable long-term outcome [7].

The diagnosis of ADEM should be readily considered whenever there is a close temporal relation between an infection or a vaccination and the subacute, polysymptomatic onset of neurological deficits. In some cases, the diagnosis may not be obvious and may require additional tests among which brain MRI. Lesions patterns more frequently encountered in ADEM include the precocious detection of widespread, bilateral, multifocal or extensive (>50% of total volume) demyelination lesions of white matter, especially in periventricular areas and brainstem, with or without gadolinium enhancement. They can be associated with lesions of grey matter (basal ganglia and thalamus) [8]. Distinction between ADEM and multiple sclerosis is difficult when previous demyelinating activity is absent, that is why a follow-up MRI is highly warranted.

Cerebro-spinal fluid analysis is not useful for ADEM diagnosis but is usually performed to rule out any acute infectious meningo-encephalitis. It may reveal elevation of albumin and proteins levels associated with mild lympho-monocytic pleocytosis. Oligoclonal band may be present, especially in adult cases, but only transiently [3]. No pathogen can be detected in cerebro-spinal fluid by specific culture or PCR detection.

As there is no pathognomonic clinical sign nor specific paraclinical test to unequivocally diagnose ADEM, the diagnosis has to be made by exclusion of a number of possible differential pathologies of central nervous system. The most important and most common are multiple sclerosis, infectious meningo-encephalitis (with sepsis and pathogen detected in cerebro-spinal fluid), inflammatory and vascular meningo-encephalitis with multifocal lesions (Behçet’s disease, neurosarcoidosis, antiphospholipid antibody syndrome, systemic lupus erythematosus, neoplasia such as lymphoma or metastasis of systemic malignancy), and inherited encephalopathies (MELAS, adrenoleucodystrophy) [9]. As all these possible diagnoses have been excluded in our patient, ADEM diagnosis was thus considered; in addition, histopathological features were not compatible with encephalopathies due to vitamin deficiency such as cerebral beriberi or Wernicke’s encephalopathy (B1) or pellagra (PP) [10,11]. Esomeprazole treatment does not seem to be involved either as no similar case was reported until now (except isolated acute confusion).

Once ADEM is diagnosed, the therapeutic aim is to shorten the central nervous system inflammatory reaction as quickly as possible and as aggressively as necessary. Despite the lack of controlled clinical trials, intravenous high-dose corticosteroids (from 3 to 8 g of methylprednisolone) are widely accepted as first-line treatment based on empiric and observational evidence [12]. Several alternative therapies should be considered in absence of clinical effect or in case of relative or absolute contraindications for corticosteroids: high-dose intravenous
immunoglobulin, plasmapheresis, immunosuppressive agents (mitoxantrone, cyclophosphamide). With the immediate use of high-dose steroids, the long-term prognosis of ADEM has changed dramatically with a functional and cognitive full recovery in 50 to 75% of cases between one and six months. Neurological sequels are reported in 15 to 30% of patients and are usually minor [3]. Mortality rate can vary widely depending on considered studies and can reach 40% in ADEM induced by measles. However, it seems to decrease especially due to the dramatic decrease of wild-type measles infections because of efficient vaccinations [4]. The most recent publications report a mortality rate of about 5% [3]. Without aggressive treatment, ADEM can evolve to extensive hemorrhages and necrosis lesions (acute hemorrhagic leuko-encephalitis [AHLE]) with a dramatically poor prognosis as death rapidly occurs due to massive cerebral oedema and/or brainstem lesions [13,14].

The psychiatric background and the lack of evidence for a recent infection are responsible for the delayed diagnosis in our patient. It is possible that the incoercible vomiting was in fact a viral gastro-enteritis, which may have been constituted the first immune response of the ADEM despite normal inflammation markers. Endogenous hypercortisolism has the same effects than corticosteroids treatment and induces an involution of lymphoid tissue mass associated with lymphopenia, each responsible for a relative immuno-deficiency and an increased susceptibility to infections. After successful cure, development or exacerbation of inflammatory and/or autoimmune diseases are classically when there is a temporal relation with an infection or a vaccination. Brain MRI constitutes a helpful tool in order to confirm the ADEM diagnosis and should be considered each time there is an atypical neurological presentation, especially when there is a temporal relation with an infection or a vaccination. Brain MRI constitutes a helpful tool in order to confirm the diagnosis but must not delay the aggressive treatment based on intravenous high-dose corticosteroids regimen.

4. Conflict of interest statement

None.

References