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CASE REPORT

Limbic encephalitis as a relapse of Whipple's disease with digestive involvement and spondylodiscitis

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Abstract

Introduction Many clinical manifestations can be related to *Tropheryma whipplei* infection.
Case report We report a *Tropheryma whipplei* limbic encephalitis developed as a relapse of classical Whipple's disease.
Discussion This case is to the best of our knowledge the first proof of the effective brain–blood barrier crossing of both doxycycline and hydroxychloroquine as demonstrated by direct concentration monitoring on brain biopsy.

Keywords *Tropheryma whipplei* · Whipple's disease · Limbic encephalitis · Emerging infectious disease

Introduction

Whipple's disease (WD) is a rare and polymorphic infectious disease due to *Tropheryma whipplei* (TW), therefore, diagnosis and treatment are often difficult [1].

We report a TW limbic encephalitis, confirmed by both PCR and immunohistochemistry on cerebral biopsy, developed as a possible relapse of classical WD.

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Report of a case

A 47-year-old man was admitted for abdominal pain, digestive haemorrhage and anaemia. Moreover, history revealed he had also been complaining of diffuse joint and lower back pains for a few years. Biological data were normal apart from low haemoglobin. Digestive endoscopy showed duodenojejunitis. Biopsy showed PAS-stained macrophages. WD was confirmed with a positive *T. whipplei*-specific immunohistochemistry (Fig. 1a).

The patient had no clinical neurological involvement. Brain magnetic resonance imaging (MRI) showed non-specific white matter lesions in both frontal lobes (Fig. 2a). CSF was normal, with a negative TW PCR.

Full body computed tomography scan revealed mesenteric adenitis. Lumbar MRI showed L1–L2, L3–L4 and L4–L5 spondylodiscitis and bilateral sacroiliitis. Transthoracic echocardiography was normal.

Doxycycline 100 mg twice a day associated with hydroxychloroquine 200 mg three times a day was initiated. The patient's condition promptly improved, as well as bone imaging. Hydroxychloroquine and doxycycline blood levels were regularly evaluated and initially considered as efficient. Hydroxychloroquine was discontinued after a 12-month course and doxycycline was pursued alone.

Five months later, the patient was readmitted for recurrence of digestive bleeding and probable epilepsy. Last doxycycline plasmatic concentration was considered being insufficient (1 µg/mL). Clinical examination revealed confusion,

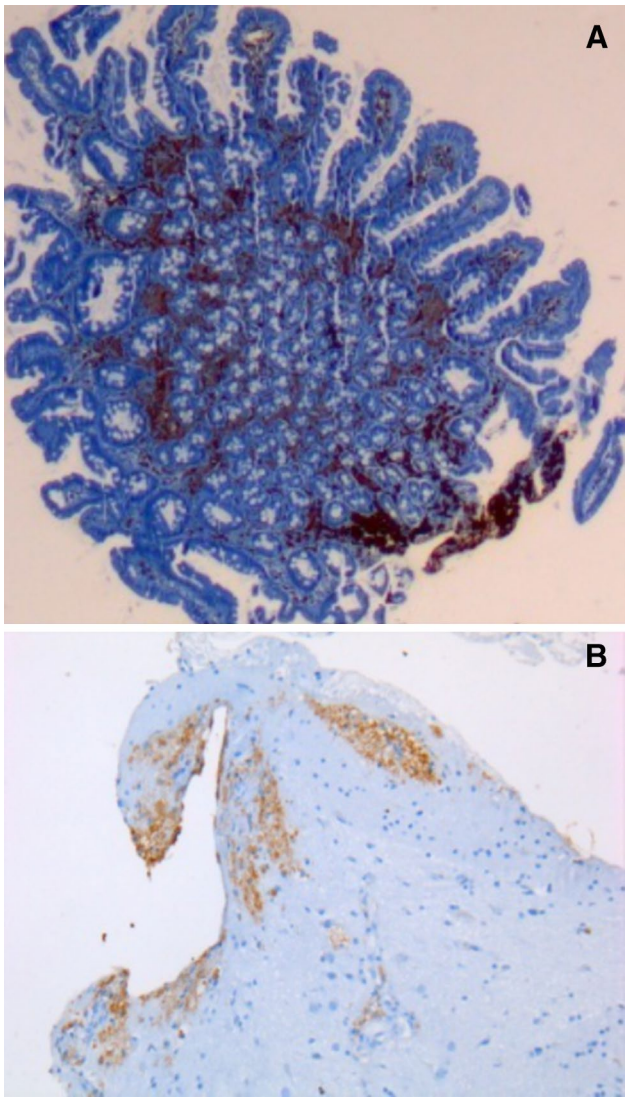

Fig. 1 Histological analysis. Histological analysis of a duodenal biopsy (**a**) and a brain biopsy (**b**) using the detection of *Tropheryma whipplei* with polyclonal rabbit antibody and Mayer's haematoxylin counterstaining (original magnification ×50)

supranuclear ophthalmoplegia, cognitive impairment, anterograde amnesia and ideomotor apraxia. He weighed 120 kg which was increased by 15 kg compared to previous evaluation. He had left shoulder pain. X-ray revealed fracture and posterior luxation of the humeral bone as commonly seen after generalised tonico-clonic seizures.

Brain MRI (Fig. 2b) showed hyperintensities in medial temporal lobes, hippocampi, caudate nucleus, and frontal lobes, consistent with limbic encephalitis.

A brain 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) scan was performed (Fig. 2d) and revealed an internal temporal hypermetabolism associated with frontal and bilateral temporal hypometabolism consistent with limbic encephalitis. Interictal EEG showed fronto-temporal slow waves without paroxysms. CSF showed no cellular reaction (9 cells/mL, PAS reactivity was not assessed) and PCR for TW was negative. A diagnosis of autoimmune limbic encephalitis was first suggested and intravenous immunoglobulin was administered without improvement at 1 month. According to the National Reference Center for WD, the patient was started on ceftriaxone 2 g twice daily, associated with doxycycline 300 mg daily and hydroxychloroquin 600 mg daily.

To precise the etiologic diagnosis, the patient finally underwent brain biopsy of the temporal lobe revealing T-cell lymphocytes and histiocyte infiltration. Immunohistochemistry and PCR performed on brain biopsy confirmed TW involvement (Fig. 1b). Hydroxychloroquine (1.1 µg/mL) and doxycycline (2.3 µg/mL) concentrations were measured on brain biopsy.

Cognitive functions of the patient quickly improved; no more digestive bleeding occurred. Ceftriaxone was stopped at week 8. Brain MRI 3 months later showed improvement (Fig. 2c). Doxycycline and hydroxychloroquin were prolonged for unspecified length of time. Plasmatic concentrations of these treatments were determined and considered within therapeutic range (doxycycline plasmatic concentrations being > 5 µg/mL). After 24 months of therapy, no sign of relapse occurred.

Discussion

WD is an infectious disease with a wide spectrum of clinical findings. Enteric involvement in WD is a common feature. In our case, initial presentation with enteric haemorrhage is unusual and no other cause of enteric bleeding was identified. Histological involvement with positive PAS staining, specific immunohistochemistry and the improvement of digestive bleeding following antibiotics introduction are in favour of enteric WD. joint swelling and arthritis is also a common feature of systemic WD, but few cases of spondylodiscitis or sacroiliitis are described in the literature [1].

Neurological manifestations are reported in 7–43% of cases [2], but are unspecific except for the pathognomonic oculomasticatory myorhythmia. Seizure, dementia, meningitis, encephalitis, recent weight gain related to hypothalamic dysfunction, and psychiatric disorders are described as neurological manifestations of WD [1–3]. Neurological relapses after treatment have also been described [1–4]. Diagnosis of neurologic involvement of WD can be difficult. In our patient, there initially was no clinical or imaging sign of cerebral involvement on the MRI. Brain MRI has sometimes been reported to show no anomaly in patients with neurological symptoms and proved neurological TW infection; therefore, an unsuspicious brain MRI in case of neurological symptoms cannot rule out neurological TW infection [5].

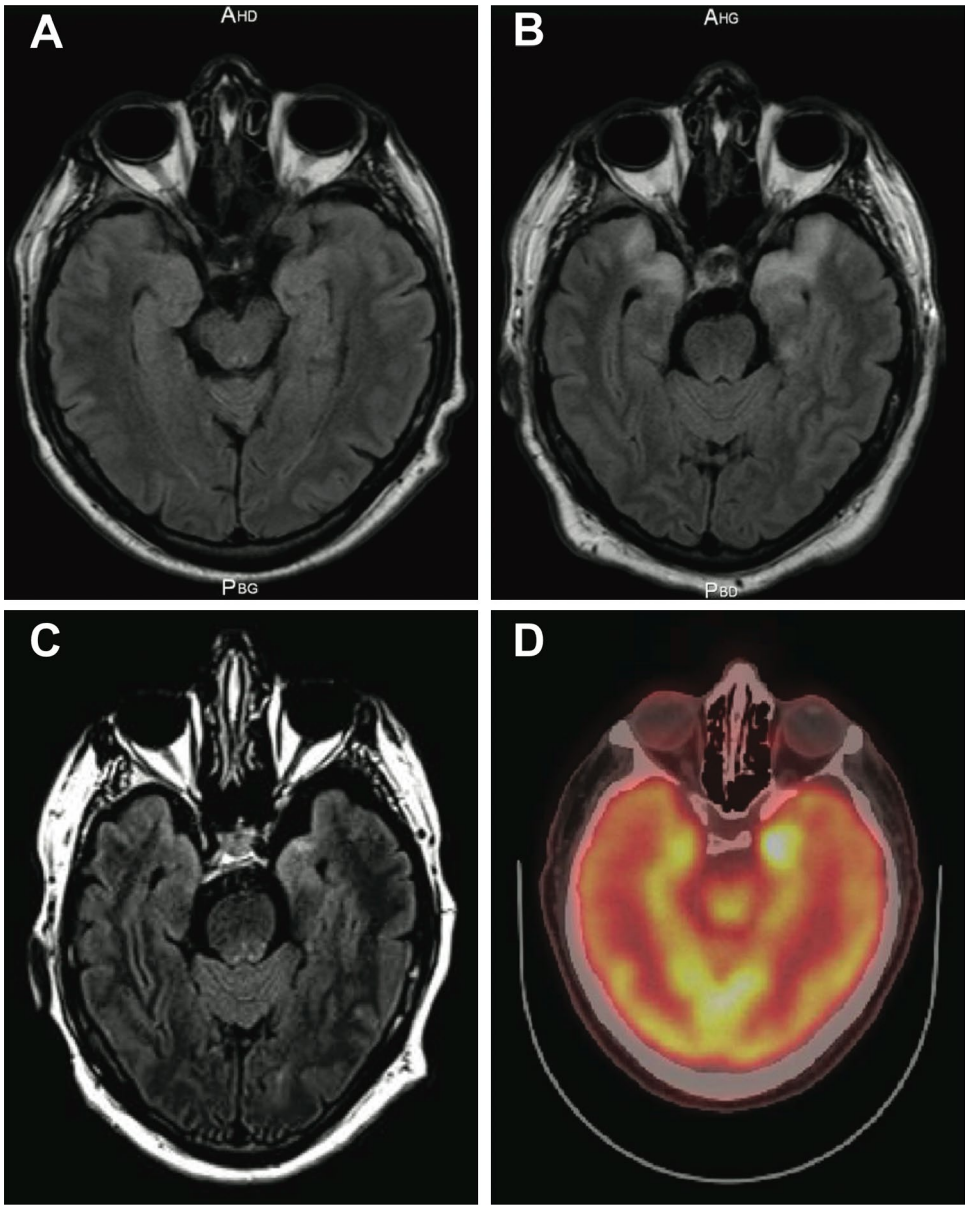

Fig. 2 Brain imaging. **a** Axial T2-weighted fluid-attenuated inversion recovery brain magnetic resonance imaging, at initial presentation. **b** At relapse, apparition of hypersignal localised to the hippocampi and the temporal poles. **c** After 3 months of treatment optimization. **d** Axial brain PET scan at relapse. Left internal temporal lobe hypersignal

In the literature, brain MRI findings can be focal-enhancing T2 signal intensity without restricted diffusion and without mass effect. Thalamus, hypothalamus, periaqueductal grey matter, and basilar telencephalon are frequently involved [5]. In a previously described case of limbic encephalitis related to WD, brain MRI findings were enhancing T2 signal intensity involving the medial temporal lobes and amygdalae [4].

Repeated analyses of CSF samples using PCR are recommended in the management of patients with WD, having being proved as a good indicator of neurological TW infection in the absence of previous antibiotic treatment [6, 7]. These analyses were repeatedly negatives in our patient and two hypotheses could be raised: (1) effect of previous antibiotic treatment, doxycycline, being administered when CSF was analysed; (2) lack of sensibility of the PCR employed. Indeed, in a previous review of isolated cerebral TW infection, Mohamed et al. reported abnormal CSF findings in only 11/23 patients [2]. Moreover, only two of seven patients had positive TW PCR on CSF. Therefore, if a positive PCR is a strong argument for neurological TW infection, a negative one cannot exclude this diagnosis. When the suspicion is high, stereotaxic biopsy guided by radiological findings should be performed.

Limbic encephalitis is often considered paraneoplastic, autoimmune or due to infectious diseases such as HSV1 infection [8]. WD should be figured among such infectious causes. Seizures, short-term memory loss and cognitive impairment, and MRI abnormalities in our patient were compatible with limbic encephalitis. Limbic encephalitis is uncommon in WD and has been reported in less than 10

patients, without histopathological confirmation in most of them [4]. Improvement after antibiotherapy initiation along with inefficacy of immunoglobulin therapy strongly suggests a direct location of TW in the temporal lobe, rather than an immunologically mediated mechanism, which is in accordance with the biopsy results.

Brain 18F-FDG-PET scan has been studied in limbic encephalitis, showing focal hypermetabolism [9]. This could be performed in patients with suspicion of neurological WD with normal CSF and MRI, to guide stereotaxic biopsy. Brain PET scan performance in neurological WD is not well documented, but a decrease in focal hypometabolism after antibiotic treatment was recently described [10].

Optimal treatment and follow up are still to be determined in WD. For years trimethoprim–sulfamethoxazole has been considered as the best empiric treatment for WD. Since the first successful TW culture, antibiotic susceptibility has been tested and trimethoprim–sulfamethoxazole showed a poor in vitro susceptibility confirmed by several clinical failures or relapses [7, 11].

Hydroxychloroquine associated with doxycycline is now recommended for WD including osteoarticular localization, given the in vitro bactericidal activity of such association [1, 12]. Recent French recommendations (disponible for reading at http://www.mediterranee-infection.com/article.php?laref=108&titre=le-traitement-de-la-maladie-de-whipple) do not support the administration of an initial parenteral course of antibiotics in osteoarticular or neurological infections as the association of hydroxychloroquine and doxycycline was proved to be efficient in these situations [6].

Relapses or failure may be related to: (1) lack of susceptibility such as for the sulphonamides [7, 11]; (2) lack of tissue penetration, as for doxycycline considered for a long time to poorly cross the blood–brain barrier; (3) lack of compliance as already described in classic WD [7]. If the efficiency of tetracycline and hydroxychloroquine was already described in cerebrospinal infection [12], our case is to the best of our knowledge the first proof of the effective brain–blood barrier crossing of both doxycycline and hydroxychloroquine highlighted by antibiotic concentrations measured on brain biopsy. Moreover, serum therapeutic drug monitoring retrospectively revealed before the digestive and neurological relapse a low doxycycline level (1 µg/mL) while hydroxychloroquine level was in therapeutic range (1.1 µg/mL) with two explanations: (1) insufficient dosage in the context of obesity; and (2) poor compliance of the patient. If weight loss is usual in classical WD [1], weight gain tends to be a common clinical anomaly among patients with neurological involvement [3]; therefore PK/PD should be taken into account for optimal dosage regimen. Finally, this case supports a lifetime treatment of patients because of a lifetime susceptibility to TW [13].

Conclusions

This limbic encephalitis presentation highlights the wide spectrum of neurological findings in WD and the complexity of its diagnosis which sometimes requires aggressive investigations such as brain biopsy. This observation confirms that doxycycline and hydroxychloroquine should be the reference treatment of WD including in the cases of neurological involvement.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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