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Case report

Recurring aseptic meningitis after travel to the tropics: a case of Mollaret's meningitis? Case report with review of the literature

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Abstract

Recurrent aseptic meningitis in a 35-year-old caucasian woman is described. She had many attacks over a period of 9 years. The first attack occurred after travel in the tropics. In spite of extensive examinations no cause could be found for the recurrent attacks. Both the clinical presentation and characteristics of the cerebrospinal fluid are compatible with the diagnosis of Mollaret's meningitis. There is no known cure for this condition, although colchicine and indomethacin have been mentioned to relieve symptoms. In our patient, a treatment with indomethacin during the last attack resulted in a clear and rapid improvement of symptoms. Since this episode only mild relapses have occurred, all of which responded well to the same treatment. This case highlights the long time span in which attacks of Mollaret's meningitis can occur, and the spectacular benefit of indomethacin.

Keywords: Idiopathic meningitis; Mollaret's meningitis; Post-travel disease; Recurrent aseptic meningitis

1. Introduction

In 1944 Mollaret described a rare syndrome of idiopathic, benign and recurring meningitis [1]. Since then only a few cases of this syndrome have been reported world-wide [2–5].

The syndrome affects mainly adults and is characterised by recurrent episodes of high-grade fever and meningeal signs. They last several days and resolve spontaneously without any neurologic sequelae [1,6,7]. The cerebrospinal fluid (CSF) is sterile and pleocytotic. During the first 24 h neutrophils and large monocellular cells are present, later lymphocytes become predominant [6–8]. Symptom-free periods can vary from weeks to months [8]. Usually the disease lasts 3–5 years, but a case with a duration of over 28 years has been described [9,10]. The aetiology is unknown, although viral infections such as *Herpes simplex* virus type 2 have been considered [11–13]. A curative treatment does not exist, but some cases have benefited from the administration of colchicine, phenylbutazone or indomethacin [1,4,5,9,11,14,15].

2. Case report

A 35-year old caucasian woman, with a personal history of African tick fever at the age of 4, was hospitalised in our ward in April 1988. She frequently travelled to several tropical and non-tropical destinations. Two days after returning from the Philippines and Thailand she developed fatigue, low-grade fever, headaches with photophobia and generalised myalgia. A treatment with erythromycin and sodium metamizol failed to improve her condition and she was hospi-

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Table 1
Results of the CSF during consecutive attacks

	30/04/1988	07/07/1988	04/08/1988
Erythrocytes	3/mm^3	92/mm^3	<2/mm^3
Leucocytes	360/mm^3	28/mm^3	22/mm^3
Differentiation leucocytes	85% lymphocytes	22.5% neutrophils 73% lymphocytes	96% lymphocytes
	15% monocytes Remnants of cells	4.5% monocytes Remnants of cells	4% monocytes
Glucose	84 mg/dl	55 mg/dl	59 mg/dl
Protein	49 mg/dl	94 mg/dl	32 mg/dl

talised. The physical examination was normal except for photophobia and nuchal rigidity. After a few days she recovered spontaneously.

Similar episodes developed initially with an interval of 3–6 months and decreased progressively in severity. However, a new episode with the same symptoms and intensity as the first occurred after a tiring intercontinental journey, 9 years after the first attack. Nuchal rigidity was reported, but given the benign nature of the previous attacks she was not hospitalised.

During the first attacks the haematological examination and biochemistry of the serum were normal. For the results of the consecutive spinal taps see Table 1. Agargel electrophoresis of the CSF on 30/04/1988 indicated normal proteins. Cultures of blood and CSF remained sterile (including *Mycobacteria*). Throat swabs were negative for *Adenovirus*, *CMV*, Enterovirus, *Herpes simplex* virus, Parainfluenza virus, Respiratory Syncytial virus or Rhinovirus. Darkfield examination of urine could not detect *Leptospira* sp. Three sputum samples were negative for acid fast bacilli. Tuberculin skin testing was negative. Antinuclear factor was negative and angiotensine 1 converting enzyme was not increased (140 U/l). CA125, carcinoembryonic antigen and alpha fetoprotein were not increased. Cortisolaemia after an overnight fast was normal.

Antibodies against the following micro-organisms were sought for on several occasions and remained negative: *Listeria monocytogenes*, *Treponema pallidum*, *Toxoplasma gondii*, *Leptospira* sp., *Salmonella* sp., *Brucella*, *Borrelia burgdorferi*, *Ricketsia conori*, *Ricketsia mooseri*, *Ricketsia prowazeki*, *Dengue*, *West Nile* virus, *Chikungunya*, *Congo Crim* virus, Rift Valley Fever, *Ebola*, *Lassa*, *Marburg*, *Hantaan* virus, *HIV*1,2, *Adenovirus*, Q-fever, Rubella, Mumps, *Epstein–Barr* virus, Measles, *Cytomegalovirus*, *Coxsackie* B1,2,3,4,5,6, *Cryptococcus*, *Blastomyces*, *Histoplasma*, *Coccidioidomyces*, *Echinococcus*, *Fasciola*, *Filaria*, *Schistosoma*, *Taenia*, *Toxocara*, *Trichinella*, *Entamoeba histolytica*, *Giardia lamblia*, *Plasmodium falciparum*, *Plasmodium vivax*, *Trypanosoma brucei*, *Trypanosoma cruzi* and *Leishmania*. Only serology against *Mycoplasma pneumoniae* indicated high and changing values during the first months of 1988 (Table 2).

A CT-scan of the brain with and without administration of intravenous contrastmedium was normal on two occasions. The chest X-ray and ultrasound examination of the heart were normal. X-ray of the sinuses and an orthopantomographic examination of the teeth could not detect any source of infection.

During the first episodes the treatment was mainly symptomatic. Because of a rise in the serology against *M. pneumoniae* a treatment with erythromycin 1 g tid was given for 2 weeks in July 1988. This did not prevent recurrence of attacks. Because of the severity of the last attack a narcotic analgesic had to be administered, but it was ineffective. Colchicine was given 0.5 mg every 2 h up to a total dose of 2.5 mg and resulted in vomiting and diarrhoea, but did not improve the initial symptoms. Only indomethacine 50 mg every 4 h proved to be effective. The patient felt fully recovered after 3 days. So far only mild relapses have occurred, all of which responded very well to indomethacin.

3. Discussion

The recurring attacks of Mollaret's meningitis usually abide after 3–5 years, although cases of longer duration have been described [9,10]. In our patient the problem lasted for at least 9 years.

In most but not all reported cases the attacks are accompanied by high fever [1,9]. In our patient only a low-grade fever was observed.

A treatment against *M. pneumoniae* was given because of an evolution of the serologic values against *Mycoplasma*. In acute meningitis caused by *M. pneumoniae* a mononuclear cell reaction in the CSF is observed, as was also the case in our patient. However, recurrent meningitis caused by *M. pneumoniae* is not described [16,17].

Table 2
Mycoplasma pneumonia serology

02/05/1988	07/07/1988	04/08/1988
1:200	1:400	1:100

The aetiology of Mollaret's meningitis is unclear: in some patients DNA of *H. simplex* virus type 2 has been found in the CSF [12,13]. We could not detect a viral aetiology in our patient. A drug induced allergy may also cause aseptic meningitis [18]. In our patient there was no drug intake which could have elicited the attacks. An abnormal production of cytokines might also be responsible for the symptoms of Mollaret's meningitis [4,7,13,18].

In some cases of suspected Mollaret's meningitis other diagnoses, such as pituitary necrosis, cranial or spinal tumours have been established [14,19]. There is indeed a long list of possible aetiologies for aseptic meningitis, but they are generally accompanied by symptoms in other organ systems [20]. Various examinations could not reveal any evidence of infection, malignancy, collagen disease, endocrine disease or disorders of the central nervous system in our patient.

A distinct feature of Mollaret's meningitis are the Mollaret's cells found in the CSF [1]. Many authors claim that these large 'endothelial cells', as Mollaret called them, are in fact monocytes [6,11]. These cells are fragile and occur mainly during the first day after onset of symptoms. [6] In our patient we could always find monocytes and twice 'cell ghosts'. The low percentage of monocytes could probably be explained by the delay in the lumbar puncture.

The treatment with erythromycin and sodium metamizol for a suspected *Mycoplasma meningitis* did not prevent recurrences, weakening this diagnostic hypothesis. Although colchicine has been described as helpful in some cases of Mollaret's meningitis, it was ineffective in our patient [15]. She responded well to a treatment with indomethacin. Ikari and Katayama improved symptoms and prevented recurrences using indomethacin [4,5]. It was highly effective in relieving symptoms in our patient, but recurrences were not prevented. Katayama found high levels of IgG, IL-6, TNF-α and PEG2 in the CSF. As indomethacin is known to interfere with these cytokines, its benefit might suggest a contribution of these cytokines to the manifestations of Mollaret's meningitis [4].

4. Conclusion

From this case we could learn that also rare, cosmopolitic diseases must be taken into account in the differential diagnosis when treating patients who return from travel in the tropics. This case is also an example of the wide spectrum of manifestations of Mollaret's meningitis: a high-grade fever is not always present and attacks can recur over a longer time than the average 3–5 years. Finally this case strengthens the evidence of therapeutic benefit of indomethacin, suggesting a role of cytokines as underlying mechanism of this syndrome.

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