Severe Hypothermia in a Patient with Cerebral Relapse of Whipple's Disease

B. Himmelmann, S. Brandner, H.H. Jung, G. Schoedon, B. Schuknecht, A. Schaffner

Abstract

The diagnosis of cerebral relapse of Whipple's disease in a 67-year-old patient was made after he presented with somnolence and severe hypothermia 4 months after discontinuing treatment with cotrimoxazole. Hypothermia is a rare hypothalamic manifestation of cerebral Whipple's disease.

Infection 2004; 32: 119–121
DOI 10.1007/s15010-004-3024-1

Introduction

Whipple's disease (WD) is a systemic disorder that includes neurologic involvement in 15% of cases [1]. Its causative agent is *Tropheryma whipplei* [2]. Diagnosis can be confirmed by periodic acid-Schiff (PAS)-positive inclusions in macrophages or PCR analysis in duodenal mucosa or cerebrospinal fluid.

Case Report

We describe a patient who presented with unexplained weight loss, diarrhea and hypoalbuminemia at the age of 63. He had been suffering from myalgias of the proximal limbs for 7 years and was treated with up to 60 mg prednisone daily because of suspected polymyalgia rheumatica. The diagnosis of WD was made by PAS stain positive macrophages in a duodenal biopsy specimen. Treatment with cotrimoxazole 160/800 mg twice daily was started. The patient's condition improved and duodenal biopsies over the next years showed regression of WD without complete clearance. Prednisone could not be reduced below 7.5 mg daily due to relapsing myalgias. At the age of 67 the patient presented with memory disorders to a neurologist. Four months earlier he had stopped cotrimoxazole treatment. Clinical examination and a CT scan showed no significant abnormalities. On the basis of an EEG, complex partial seizures were suspected and treatment with carbamazepin 200 mg daily was started. One month later the patient was admitted to our hospital with unexplained somnolence after a car accident. On admission blood pressure was 130/90 mmHg; heart rate, 52 per min and core temperature, 33.2 °C. Neurological examination showed somnolence, mutism and a slight spastic tetraparesis with a bilaterally positive Babinski's sign. An MRI revealed multiple punctuate and confluent lesions of increased signal intensity affecting the hypothalamus, fornix and the periventricular subependymal grey and white matter in a symmetric fashion (Figure 1 A). The lesions predominantly extended along the frontal horns within the caudate nucleus and along the third ventricle. Cerebral involvement of WD was proved by phagocytic cells in the cerebrospinal fluid with typical PAS-positive inclusions (Figure 1 B) and positive PCR for *T. whipplei*. Treatment with cotrimoxazole 160/800 mg twice daily and rifampicin 300 mg three times daily was started. The patient's condition improved and he was able to handle everyday activities. Hypothermia with a core temperature ranging between 31.1 and 35.4 °C (mean: 33.3 °C) persisted for 9 weeks.

The following febrile episode was attributed to catheter sepsis. Several syncopes occurred and echocardiography confirmed severe aortic stenosis with calcification. The patient developed hypotension and pulmonary edema. He was treated with vasoactive drugs and antibiotics including vancomycin 1 g, netromycin 300 mg, rifampicin 900 mg and ceftriaxone 2 g daily. Blood cultures remained negative. He died in refractory shock despite aortic valvuloplasty performed 2 weeks earlier. Autopsy of the heart revealed no signs of endocarditis. The brain autopsy showed cerebral involvement of WD macroscopically, by histological examination (Figures 1 C, 1 D) and by electron microscopy.

Discussion

The patient described suffered from gastrointestinal WD preceded by myalgia for 7 years before the diagnosis of WD was made. The clinical presentation of myalgia and arthralgia is well known in WD and precedes the diagnosis by a mean of 6.7 years [3]. Prednisone was not reduced below 7.5 mg daily because of relapsing symptoms. It remains unclear if these symptoms were due to WD or a second disorder such as polymyalgia rheumatica.

B. Himmelmann *(corresponding author)*, **G. Schoedon, A. Schaffner**
Dept. of Internal Medicine, University Hospital of Zurich, CH-8091 Zurich, Switzerland; Phone: (+41/1) 255-4653, Fax: -4445,
e-mail: barbara.himmelmann@usz.ch
S. Brandner
Institute of Neuropathology, University Hospital of Zurich, Zurich, Switzerland
H.H. Jung
Dept. of Neurology, University Hospital of Zurich, Zurich, Switzerland
B. Schuknecht
Institute of Neuroradiology, University Hospital of Zurich, Zurich, Switzerland

Received: February 18, 2003 • Revision accepted: July 28, 2003

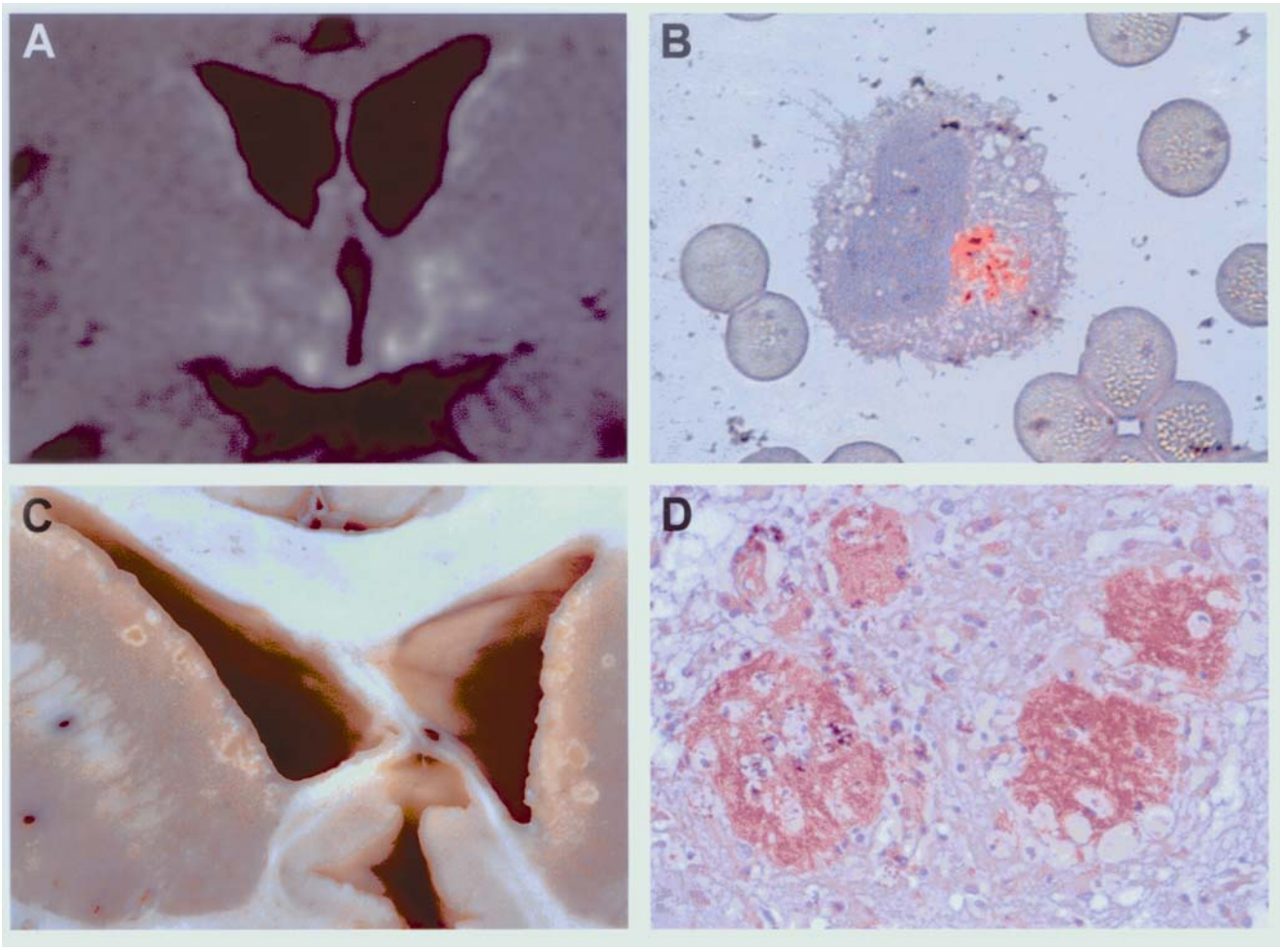

Figure 1. A. Coronal T1 weighted MRI showed nodular hypothalamic and periventricular contrast enhancement extending into the adjacent subependymal grey matter and along the floor of the third ventricle and fornix. B. Cerebrospinal fluid examination showed phagocytic cells with PAS-positive inclusions. C. Frontal sections of the formalin fixed brain revealed multiple lesions surrounded by a bright rim. They were mainly distributed along the wall of the lateral ventricles but were also found in the hypothalamus. D. Histological examination of the paraffin embedded sections revealed numerous plaque-like and PAS-positive deposits. Closely associated with these plaques were macrophages filled with small PAS-positive particles.

At the age of 67 the patient presented with a cerebral relapse of WD with cognitive changes and persistent hypothermia. Treatment had been stopped for 5 months when the first signs of cerebral involvement appeared.

The diagnosis of cerebral WD remains a problem, even though neurologic symptoms occur in 15% of cases [1]. It has been shown that CNS involvement diagnosed by PAS-positive cells in the cerebrospinal fluid examination are common in patients with WD without neurological symptoms [4]. In our patient further symptoms included seizures, somnolence and severe hypothermia. A review of 84 cases of cerebral WD showed that cognitive changes and altered levels of consciousness are frequent and occur in 71% and 50% of patients with cerebral manifestations, respectively [5]. In this series hypothermia was not described as a hypothalamic manifestation of WD. It had been described previously but is very rare [6, 7]. A propensity for cerebral manifestations of WD to affect midline structures has previously been described by MRI, including signal intensity changes in the hypothalamus [8]. Off midline lesions were observed to affect the subcortical white matter, and did not take up contrast nor exhibit space-occupying effects [9]. The radiologic findings in this patient are in agreement with the literature with respect to their central location. However, the nodular subependymal extension, the striking symmetry and the lack of subcortical white matter involvement differ from previous reports.

References

1. Marth T, Raoult D: Whipple's disease. Lancet 2003; 361: 239–246.
2. Relman DA, Schmidt TM, MacDermott RP, Falcow S: Identifica-

tion of uncultured bacillus of Whipple's disease. N Engl J Med 1992; 327: 293–301.
3. Puéchal X: Whipple's disease and arthritis. Curr Opin Rheumatol 2001; 13: 74–79.
4. Von Herbay A, Ditton HJ, Schuhmacher F, Maiwald M: Whipple's disease: staging and monitoring by cytology and polymerase chain reaction analysis of cerebrospinal fluid. Gastroenterology 1997; 113: 434–441.
5. Louis ED, Lynch T, Kaufmann P, Fahn S, Odel J: Diagnostic guidelines in central nervous system Whipple's disease. Ann Neurol 1996; 40: 561–568.
6. Bleibel JM, Cabane J, Kardouss J, Wechsler B, Poisson M, Buge A: Maladie de Whipple a forme hypothalamique. Ann Med Intern 1983; 134: 723–727.
7. Gerard A, Sarrot-Reynauld F, Liozon E, Cathebras P, Besson G, Robin C, Vighetto A, Mosnier J, Durieu I, Vital Durand D, Rousset H: Neurologic presentation of Whipple disease. Report of 12 cases and review of the literature. Medicine 2002; 81: 443–457.
8. Schider P, Trattnig S, Kollegger H, Auff E: MR of cerebral Whipple disease. Am J Neuroradiol 1995; 16: 1328–1329.
9. Brown AP, Lane JC, Murayama S, Vollmer DG: Whipple's disease presenting with isolated neurological symptoms. J Neurosurg 1990; 73: 623–627.