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Meningovascular form of neuroborreliosis: similarities between neuropathological findings in a case of Lyme disease and those occurring in tertiary neurosyphilis

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Summary. Recent observations have delineated the neurological manifestations of Lyme disease, but, to our knowledge, no detailed neuropathological study from autopsy cases has been reported. In this report we describe the neuropathological findings in a case of Lyme neuroborreliosis. The chronic meningitis, the occlusive meningovascular and secondary parenchymal changes that we found are similar to those occurring in the meningovascular form of neurosyphilis. Thus, we suggest that the case described here represents the meningovascular form of tertiary Lyme neuroborreliosis.

Key words: Borrelia infections – Central nervous system diseases – Lyme disease – Heubner's arteritis – Neuropathology

The spirochetal etiology, epidemiology and clinical course of Lyme disease are well established [2, 3, 5, 12, 21, 22]. Based on similarities with syphilis, Pachner and Steere [19] have classified the clinical manifestations of *Borrelia burgdorferi* infections into three stages. Stage I of the illness is characterized by a localized skin lesion, the erythema chronicum migrans. In stage II the disease becomes generalized and some patients develop a "tick-borne meningoradiculitis" first described in Europe [1, 8, 9]. It is characterized clinically by meningitis, cranial neuritis and radiculoneuritis [19] and morphologically by lymphocytic infiltration of the leptomeninges [7]. In stage III, the patients can develop neurological manifestations of parenchymal brain involvement [10, 13, 14, 16, 20]. Histological examination of a small number of brain biopsy specimens showed proliferation of microglial cells in the cortex without inflammatory infiltrates [7, 20]. Borrelia spirochetes were cultured from the autopsy brain tissue of two demented patients [14].

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In the peripheral nervous system recent studies suggest an angiopathic etiology for the nerve damage [15]. To our knowledge, no detailed neuropathological study of the central nervous system from autopsy cases of Lyme disease has been described. Here we report the neuropathological findings of a case of Lyme neuroborreliosis, which provides support for the notion that the development of the disease is characterized by three distinct stages.

Case report

A 50-year-old male patient presented in November 1982 at the age of 47 with a spastic left lower limb paresia, with generalized hyperactive tendon reflexes. CSF showed a predominantly lymphocytic pleocytosis (212/ml; 93% lymphocytes) and an elevated protein level (1290 mg/l). After corticotherapy for 15 months, the patient gradually improved. In February 1984, he was readmitted because of the appearance of multiple cranial nerve dysfunction. After partial improvement, in July 1984, the patient developed a severe right hemiparesis and over the next 3 days, a superimposed left hemiparesis with ventilatory failure. The CSF pleocytosis and the higher protein concentration persisted. The patient received 1.5 g/day of intravenous Amoxicillin for 3 weeks and a high dose of intravenous dexamethasone for 3 months. Following bilateral pneumonia in June 1985, which was treated by 1.5 g/day of intravenous Amoxicillin for 1 week the patient died. The diagnosis of neuroborreliosis was established serologically by the determination of the immunofluorescent antibody titer (IFAT). In December 1982 CSF titers were 128 for IgG IFAT (normal: > 4) and 8 for IgM IFAT (normal: > 4). In September 1984 the CSF titer was 256 for IgG IFAT (normal: > 4), and the serum titer 512 for IgG IFAT (normal: > 64). At this time, the IgM IFAT in both the serum and CSF was negative. Tests for VDRL (Veneral Disease Research Laboratory test), anti-nuclear antibodies and for rheumatoid factor were negative. Cultures for bacterial and fungal infections, as well as serology for a large number of viral infections proved to be negative.

Methods

Twenty representative samples from the formalin-fixed brain and spinal cord were embedded in paraffin, and 5-μm sections were

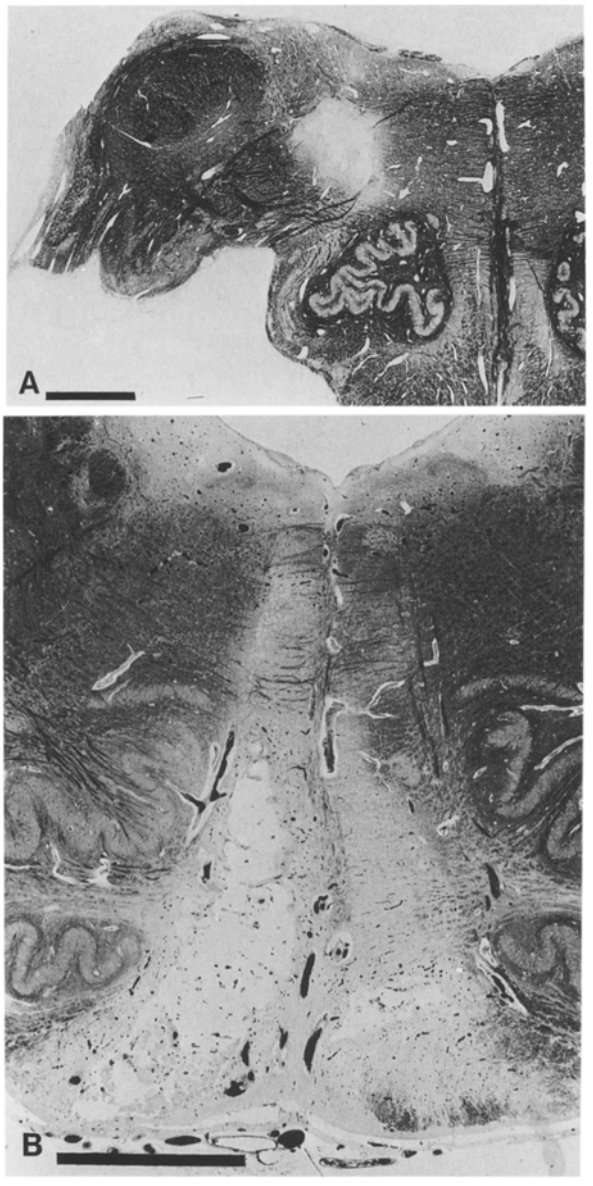


Fig. 1. Photographs of transverse paraffin sections through the rostral part of the medulla oblongata (**A**) and through the midolivary region (**B**), illustrating the well-demarcated small infarcts. Loyez stain; bars represent 5 mm

stained with Nissl, haematoxylin-eosin, Van Gieson luxol fast blue, Van Gieson elastin, phosphotungstic acid haematoxylin, PAS, Loyez and Prussian blue stains. The blocks from the medulla oblongata were serially sectioned and stained alternatively by the haematoxylin-eosin and Van Gieson luxol fast blue techniques. The Warthin-Starry silver impregnation technique was used to demonstrate the spirochete of *Borrelia burgdorferi*. A transverse section of the medulla oblongata taken from the brain of an otherwise healthy patient who died after head injury was used as negative control, and a section taken from the frontal cortex of an autopsy case of general paralysis was used as positive control. The Gram, Ziehl-Neelsen and Grocott's methenamine silver stains were used to search for other bacterial and fungal elements. Sections from cases with known Staphylococcal, mycobacterial and fungal (Aspergillus) infections were used respectively as positive controls. Paraffin sections (5 μm) through the medullary level were stained immunohistochemically using polyclonal antibodies against herpes simplex viruses I (HSV I) and II (BioGenex Laboratories, HistoGen PAP Herpes I and II HP086-5P PR), and monoclonal antibody against cytomegalovirus (CMV) (Dako: M 757; clone CCH2). A section taken from the brain of a patient who died of AIDS, in which the neuropathological and immunohistochemical study revealed a concomitant HSV I and CMV encephalitis, was used as positive control.

Results

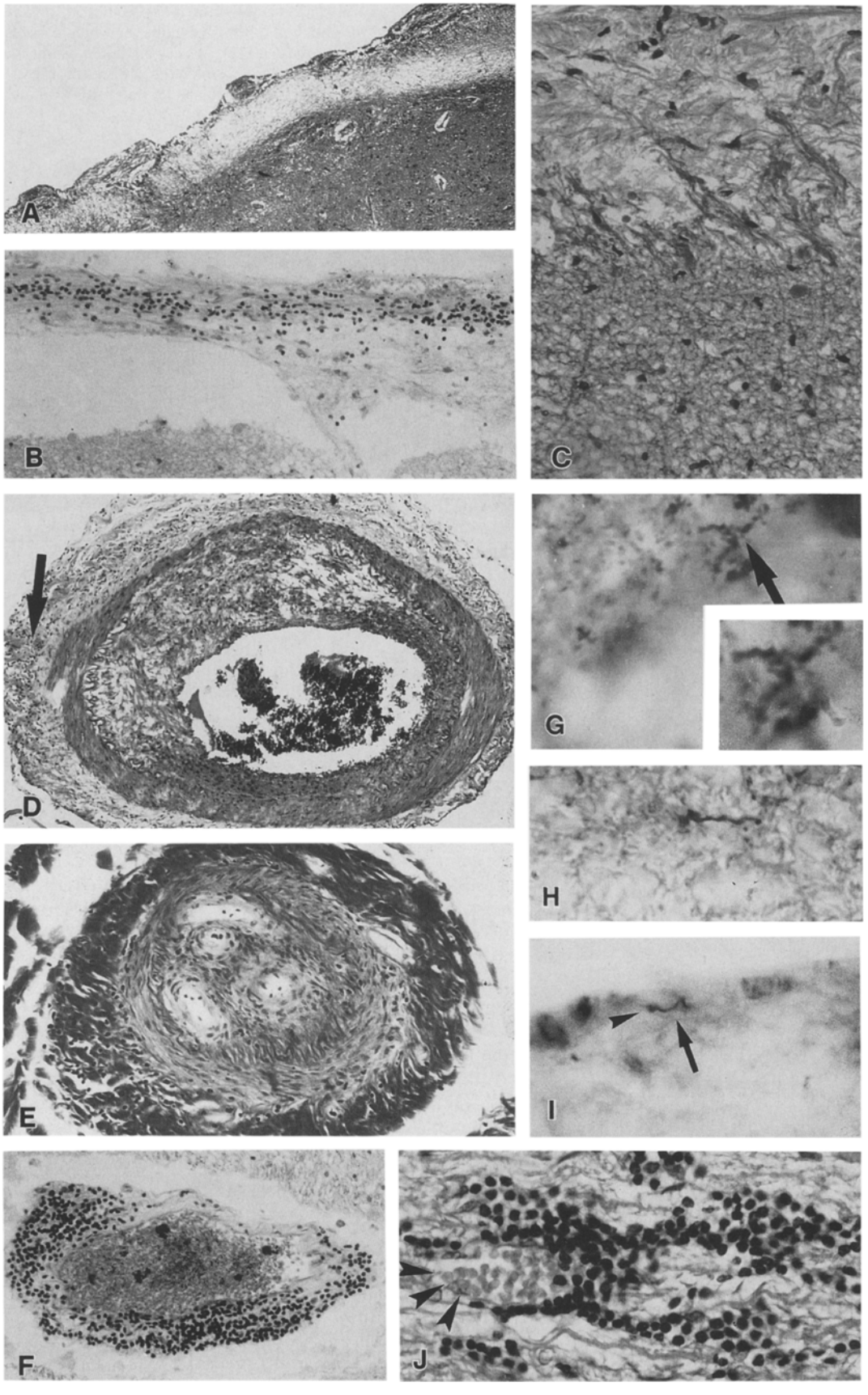
General autopsy revealed a bilateral bronchopneumonia and a discret atheromatosis without stenosis of the coronary arteries.

Macroscopical examination of the CNS

The fixed brain weighed 1740 g, and showed discrete thickening and opacity of the leptomeninges accentuated at the base of the brain. Transverse sections of the brain stem showed a fine granular appearance of the ependyma, especially on the floor of the fourth ventricle, and two small infarcts situated in the medulla oblongata (Fig. 1 A, B). The first (5 mm in diameter) was localized in the tegmentum (Fig. 1 A), in the territory of the superior arterial branches of the left lateral medullary fossa, originating from the basilar artery. The second (Fig. 1 B), more caudally situated infarct ($8 \times 7 \times 5$ mm), destroyed territory of the paramedian arteries originating from the anterior spinal artery.

Microscopical examination of the CNS

The histopathological changes that we found were especially localized at the level of the medulla oblongata. The macroscopically visible ependymal granulation appeared histologically as irregular nodular protrusions of subependymal glia (Fig. 2 A). The leptomeninges showed mild fibrosis and a chronic infiltration (Fig. 2 B), consisting of lymphocytes and rare plasma cells. The pia mater was firmly attached to the medullary surface and outgrowth of neuroglia through breaks in the pia mater was seen (Fig. 2 C). The medium- and small-sized leptomeningeal arteries at the level of the medulla oblongata showed important fibroblastic thickening of the intima (Fig. 2 D), narrowing the vascular lumen. The elastic lamina sometimes showed duplication, but otherwise was spared. A discrete fibrosis or localized thinning of the media was sometimes observed, but generally it remained intact. In the adventitia, there was an excess of fibrous tissue often with lymphocytic infiltrates. Complete obstruction of some leptomeningeal vessels by organized thrombus was found (Fig. 2 E), leading to the small medullary infarcts described above. The leptomeningeal perivascular lymphocytic infiltration followed vessel branches into the medullary parenchyma along the Virchow-Robin spaces. Only in a few of them was partial lymphocytic infiltration of the vessel wall also seen (Fig. 2 F). The parenchymal changes consisted of the two small, kystic, anemic infarcts (Fig. 1 A, B). On serial sections of the medulla oblongata, two microglial nodules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were found, both localized in the region of the spinal trigeminal nuclei and tracts. The Wallerian degeneration of nerve fiber tracts interrupted at the level of the medulla oblongata was studied in detail, and described in a report on the visualization of the myelinated pathways in the human brain [18]. The left trigeminal nerve showed discrete perivascular and interstitial lymphocytic infiltrations (Fig. 2J). Focal myelinoaxonal loss and fibrosis in some cranial nerves and in the radicular portion of some spinal nerves with patchy distribution were also observed.

We did not find bacterial or fungal infection on the histological sections, nor could we demonstrate viral antigens of HSV I, II and CMV immunohistochemically. With the silver impregnation method, we found coiled spirochetes, morphologically similar to those of *Borrelia burgdorferi* (Fig. 3G–I). They were few in number and were localized to the medullary leptomeninges and ependymal regions of the fourth ventricle. The negative control section was free of such silver-impregnated elements.

Discussion

The meningovascular changes found in our case, in association with chronic leptomeningitis and granular ependymitis, are similar to those occurring in the meningovascular form of neurosyphilis, described by Heubner as "endarterities obliterans" [11]. It is an affection of the leptomeningeal arteries, characterized by intimal proliferation which, by gradually narrowing the lumen tends to cause thrombosis with resultant anemic infarction.

A number of midline brain stem syndromes are known to be caused by meningovascular syphilis [17]. Heubner's arteritis was thought to be specific to syphilis, but it may also occur in incompletely treated cases of tuberculosis, influenzal, pneumococcal and other forms of chronic meningitis [6]. In the present case, the serological tests for syphilis and for viruses were normal. Cultures for the search of bacterial and fungal infections, inlcuding mycobacterial CSF cultures were negative. The positive serological reaction for *Borrelia burgdorferi* in both the blood and CSF [5], and the presence of spirochetes in tissue sections make the diagnosis of Lyme disease reasonably certain, suggesting that the meningovascular changes are due to the neuroborreliosis.

In the interpretation of clinical and neuropathological findings, it is important to consider that, like neurosyphilis, the developing spirochetal diseases may be attenuated in today's antibiotic era, and the clinical and pathological manifestations may become more subtle and difficult to recognize [4]. When the inflammatory reaction in the residual stage of Heubner's arteritis subsides following treatment, only the hyperplastic intima remains. Parenchymatous forms of neurosyphilis are uncommon and the necrotic, gummatous lesions have now practically disappeared [4].

In conclusion, the similarities between Lyme disease and syphilis are multiple. Both spirochetes are neurotropic and in both diseases the neurological manifestations occur in "stages". Not only the clinical, but also the neuropathological aspects seems to be very similar. The neuropathological changes in Stage II of the Lyme neuroborreliosis are characterized by a lymphoplasmocytic basal meningitis associated with granular ependymitis. In the tertiary stage the parenchymal involvement is determinant. As the example of our case shows, the secondary stage can turn into the tertiary stage in the form of meningovascular neuroborreliosis, where the parenchymal involvement is secondary. The essential lesion is the chronic meningitis leading to Heubner's arteritis, with resultant occlusive thrombosis and secondary cerebral infarcts. Direct invasion of the nervous tissue by the spirochetes (primary parenchymal involvement, of the tertiary stage) may explain the described clinical manifestations of parenchymal brain involvement [10, 13, 14, 16, 20]. Various combinations of vascular meningeal and parenchymal involvements certainly exist.

Fig. 2A–F. Photomicrographs showing the meningovascular changes at the level of the medulla oblongata. **A** Transverse paraffin section through the larger part of the fourth ventricle showing the severe granular ependymitis. Haematoxylin-eosin, ×30. **B** Chronic leptomeningitis. Cresyl violet, ×120. **C** Chronic inflammation leading to leptomeningeal fibrosis with glial outgrouwths. Haematoxylin-eosin, ×192. **D** This leptomeningeal artery shows fibroblastic thickening of the intima narrowing the vascular lumen. Note the proliferation of the adventitia with lymphocytic infiltration (*arrow*). Cresyl violet, ×48. **E** Leptomeningeal artery localized in the left medullary fossa showing recanalized thrombosis. Note the fibrous thickening of the adventitia. Haematoxylin eosin, ×75. **F** Lymphocytic infiltration of the wall of a leptomeningeal vessel entering into the medulla oblongata. Haematoxylin-eosin, ×120. **G–I** Photomicrographs showing the silver-impregnated coiled spirochetes, morphologically similar to the *Borrelia burgdorferi*. Warthin-Starry stain, ×1200. **G** *Arrow* points to the spirochetes represented in the *inset* at higher magnification (×1600). *Arrow* in **I** poitns to a fragment of spirochete in the ependymal layer with the typical bud (*arrowhead*). **J** Photomicrograph showing lymphocytic infiltration in the left trigeminal nerve, localized around and near a small vessel (*arrowheads*). Cresyl violet, ×300

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