Neurobrucellosis Associated with Syndrome of Inappropriate Antidiuretic Hormone with Resultant Diabetes Insipidus and Hypothyroidism

Giuseppe Sturniolo,1 Placido Mondello,1 Salvatore Bruno,2 Orsola Elena Bonfatto,2 Sabrina Frattima,1 Antonio Albanese,1 Roberta Restivo,3 Giuseppe Liberti,3 Paolo Pasquali,4 and Cinzia Marianelli4*

Department of Infectious Diseases, G. Martino Hospital, University of Messina, Messina, Italy; Department of Infectious Diseases, Cutroni Zodda Hospital, Barcellona Pozzo di Gotto, Italy; Department of Infectious Diseases, Cannizzaro Hospital, Catania, Italy; and Department of Food Safety and Veterinary Public Health, Istituto Superiore di Sanità, Rome, Italy

Received 7 April 2010/Returned for modification 21 June 2010/Accepted 2 August 2010

Neurological involvement of the central nervous system in brucellosis is uncommon. We describe a rare case of meningoencephalitis due to Brucella melitensis infection, associated with the syndrome of inappropriate antidiuretic hormone secretion and leading to diabetes insipidus and hypothyroidism. Neurobrucellosis, although rare, should be considered in cases of neurological disease of unknown etiology.

CASE REPORT

A 17-year-old male patient presented with headache, backache, fever, and marked asthenia. After 10 days, his headache worsened and vomiting occurred. He was admitted to the Department of Infectious Diseases of the Cutroni Zodda Hospital, Barcellona P.G., Sicily, Italy. Neurological examination upon admission revealed diffuse hyperreflexia, nuchal rigidity, and hyposthenia of both legs. Laboratory examinations revealed leukopenia with lymphocytosis and severe hyponatremia (118 mEq/liter) with reduced serum osmolality (241 mOsm/kg) and elevated urine osmolality (455 mOsm/kg). Renal, thyroid, and adrenal functions were normal. These data were consistent with the diagnosis of syndrome of inappropriate antidiuretic hormone secretion (SIADH). The patient was treated with intravenous NaCl (3%) and water restriction. His plasma sodium concentration increased to 125 mmol/liter.

Analysis of the cerebrospinal fluid (CSF) showed pleocytosis (175 white blood cells/mm3, predominantly polymorphonuclear leukocytes), low glucose levels (11 mg/dl), and high protein levels (1,020 mg/dl), indicating a disruption of the blood-brain barrier. Both serum and CSF samples tested negative for Neisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae antigens. At admission, the standard Brucella tube agglutination test (Wright test) result was also negative (titer < 1:100). This result was further confirmed by the slide agglutination rose bengal test (4). While waiting for microbiological results, the patient was treated with ceftriaxone (4 g/day), ampicillin/sulbactam (12 g/day), and dexamethasone (16 mg/day).

Suspected Brucella colonies were isolated from both blood and CSF 7-day cultures and identified following standard procedures (4). Biochemical and agglutination tests identified the pathogen isolated from both body fluids as Brucella melitensis biovar 3. A diagnosis of meningoencephalitis due to Brucella infection was made, and the therapy was promptly modified as follows: ampicillin-sulbactam was discontinued, and chloramphenicol (4 g/day), rifampin (900 mg/day), and trimethoprim (Trimetoprim)-sulfamethoxazole (1,600/320 mg/day) were started. The serum agglutination test for Brucella bacteria was repeated a week after admission: the patient had seroconverted (anti-Brucella antibody titer, 1:320).

To characterize the isolate at the molecular level, rpoB sequencing and typing by the multiple-locus variable-number repeat analysis of 16 loci (MLVA-16) were performed as previously described (22). The former showed the presence of a nucleotide substitution (ATC to ATA) at codon position 1249 (M1249I), identifying the isolate as Brucella sp. rpoB genotype 3. The resulting MLVA profile was as follows: 3-6-3-14-1-1-3-3-6-4-11-4-7-21-8-3. This profile was then compared both to the Brucella2009 MLVA database (http://minisatellites.u-psud.fr/MLVAnet/querypub1.php) and to our database containing previously characterized MLVA profiles originating from the area of Catania, Sicily (22). The analysis showed that the isolate in question belongs to a new genotype in the endemic area covered by our database.

Despite 20 days of treatment, symptoms persisted (fever, headache, hyponatremia, natriuresis, phosphaturia, and chloruresis). Thus, antibiotic therapy was further modified as follows: trimethoprim-sulfamethoxazole and chloramphenicol were discontinued, and tigecycline (100 mg/day) and dexamethasone (16 mg/day) were added. A contrast cranial computed tomography (CT) scan showed an enlarged posterior pituitary gland, pituitary stalk, and subarachnoid space, with hyperdensity in the basal cisterns.

Due to his clinical condition, the patient was transferred to Cannizzaro Hospital in Catania and, shortly thereafter, to the Messina University Department of Infectious Diseases. The patient had evidence of dehydration, with dry skin on both legs, and complained of excessive thirst. Fever, hypothermia, natriuresis, and chloruresis still persisted. Paresthesia in both legs...
and a consequent difficulty in walking were also present, in the absence of Lasègue’s sign. Tests revealed leukocytosis (12,300/ mm cubes), diuresis (5.5 liters per 24 h), normal serum, and low urine osmolality (275 and 195 mOsm/kg, respectively; urine specific gravity < 1.004 gm/cc). Hyponatremia persisted (110 mEq/liter), while urine and blood glucose levels were normal. These results strongly suggested endocrine and metabolic dysfunction. Specifically, diabetes insipidus (DI) was suspected. The results of a water deprivation test with vasopressin injection were consistent with central DI. Thyroid function was also tested with the following results: the serum concentration of thyroid-stimulating hormone (TSH) was 0.49 mU/liter (reference interval, 0.27 to 4.2 mU/liter) with free thyroxine (FT4) at 9.67 pmol/liter (reference interval, 12 to 22 pmol/liter). These data were compatible with a diagnosis of secondary hypothyroidism. The patient was given rifampin at 600 mg/day, tigecycline at 100 mg/day, vasopressin at 20 mg/day, and levothyroxine at 50 mg/day. Hyponatremia resolved after 3 days of therapy.

One week after admission at the Messina hospital, the patient’s chest X ray was normal. Magnetic resonance imaging (MRI) showed pathological lesions within the suprasellar, pre-pontine, and interpeduncular cisterns. Focal lesions of the spinal cord were also noted, involving the D1 and D2 vertebrae. Antibiotic therapy was, therefore, modified as follows: tigecycline was substituted with levofloxacin at 500 mg/day, doxycycline at 200 mg/day, and streptomycin at 1 g/day. Treatment with rifampin (600 mg/day) was continued.

Despite the modification of therapy, spinal fluid still revealed pleocytosis, low glucose levels (18 mg/dl), and elevated protein levels (197 mg/dl). Anti-Brucella IgG results, as detected by a commercial enzyme-linked immunosorbent assay (ELISA) kit (NovaTec Immundiagnostica GmbH, Waldstrasse, Germany), were positive; corresponding IgM results were negative. During this period, the patient suffered an episode of high fever with temporal and spatial disorientation and hyperreflexia. Antibiotic therapy was changed again; streptomycin and levofloxacin were replaced with ceftriaxone (4 g/day) and trimethoprim-sulfamethoxazole (4,800/960 mg/ day). Rapid clinical improvement followed. An MRI performed 25 days after baseline showed a reduction in pathological lesion size in the suprasellar region.

Two months after his last hospitalization, the patient was discharged with the following therapy: doxycycline at 200 mg/ day, rifampin at 600 mg/day, ceftriaxone at 4 g/day, and trimethoprim-sulfamethoxazole at 4,800/960 mg/day.

A follow-up performed 1 month after discharge showed a nor- mal CSF analysis result, with anti-Brucella IgG and IgM results both negative. Trimethoprim-sulfamethoxazole and ceftriaxone doses were reduced to 3,200/640 mg/day and 2 g/day, respectively.

A follow-up MRI performed 5 months after discharge showed no residual lesions. All neurological symptoms had resolved, and no recurrence of symptoms was registered. Anti- tuberculous therapy was then stopped. Unfortunately, DI and hypo-thyroidism persist, and the patient is still in therapy.

Brucellosis is a multisystem infection that can involve almost any organ or system, including the central nervous system (CNS), and it has a broad spectrum of possible clinical manifestations and complications; fever, night sweats, arthralgia, myalgia, and nonspecific neurological symptoms are common. Neurological involvement of the CNS has been detected in 3 to 5% of patients with brucellosis (32), but it nevertheless results in severe morbidity and is potentially life threatening (11, 37).

The clinical spectrum of neurobrucellosis is very heterogeneous and includes meningitis, encephalitis, polyradiculoneu- ritis, sensory and motor disorders, cranial nerve involvement, epilepsy, depression, brain abscess, and subarachnoid hemorrhage (28). Rarer neurological manifestations are isolated intracranial hypertension (26), Guillain-Barré syndrome (25), DI (34), and pituitary abscess (16). The SIADH, first described in 1988 (5), is a rare complication of brucellosis. The present report describes a case of brucellosis in Sicily, with neurological complications characterized by extensive involvement of the brain parenchyma, an infection which caused SIADH, leading in turn to focal neuroendocrine disturbances such as DI and hypothryoidism.

Due to its heterogeneous clinical manifestations, neurobrucellosis is easily confused with many other neurological, neurosurgical, or even psychiatric disorders (2, 9). To complicate matters, its diagnosis, requiring direct or indirect evidence of Brucella bacteria in the CSF (9, 32), is difficult to establish and frequently delayed. This is due to the fact that specific anti- Brucella antibody titers in CSF are usually low and that cultures take time and often give false-negative results (2). Moreover, the neuroimaging of neurobrucellosis may appear normal or mimic many other infectious or inflammatory conditions (3). These factors may contribute to false-negative diagnoses (6, 29). In the case described here, blood and CSF samples initially tested negative for anti-Brucella antibodies by using the Wright test which also excluded the presence of incomplete antibodies, causing false-negative reactions. The absence of seroconversion was confirmed by the slide agglutination rose bengal test. It is likely that, at the time of admission, Brucella anti- bodies were not yet detectable in the patient’s samples. It is intriguing that at admission the patient, with evident neurological symptoms, had no detectable anti-Brucella antibodies in the serum sample. It could be correlated with a slow immunological response induced by exogenous or endogenous factors which, however, were not investigated because they are beyond the scope of this report. The diagnosis of neurobrucellosis was, thus, made only a week later, when Brucella bacteria were isolated from a 7-day CSF culture. As previously reported, a delay in diagnosis, and thus also in the administration of ap- propriate antibiotic treatment, may cause neurological se- quelae (23). This may be averted in the future thanks to novel diagnostic technology, such as molecular methods (10).

The molecular characterization of this human isolate has confirmed, as previously reported (22), that in Italy the disease is associated with B. melitensis biovar 3. Small ruminants and foods derived from them are the major source of brucellosis and play a key role in the spread of infection both in cattle and in humans. The MLVA-16 technique has allowed us to identify a new genotype in the endemic area covered by our database—the area of Catania in Sicily. Further studies will be needed to evaluate possible correlations between specific genotypes and their respective pathogenic patterns.

The management of neurobrucellosis requires special atten- tion since the illness is potentially life threatening. Although no
specific guidelines are available on the duration and type of antibiotic therapy to be given in cases of neurobrucellosis, most authorities recommend a combination of two or three drugs able to cross the blood-brain-CSF barriers, such as doxycycline, ciprofloxacin, and rifampin (1, 23). Treatment should generally be continued until results of CSF analyses return to normal. Individual signs and symptoms should also be taken into account when prescribing treatment. In our case, the regimen was modified several times following developments regarding symptoms, findings, and the clinical course of the disease, and the combination of ceftriaxone, doxycycline, rifampin, and trimethoprim-sulfamethoxazole has been administered for a long period of time. Antibiotics were given for a total of 32 weeks, until the complete resolution of all neurological symptoms that were observed at the second follow-up, performed 5 months after discharge. By the end of the course of treatment, CFS analysis had returned to normal and neuroimaging showed no residual lesions. Clinical follow-up indicated that Brucella infection had indeed been eliminated, although DI and hypothyroidism still persist.

In the present case of neurobrucellosis, two temporally separate instances of endocrine and metabolic disorders occurred. The first occurred on admission, when the patient presented with a clinical picture which met the diagnostic criteria for SIADH (20). This syndrome has been reported in association with both neoplastic and nonneoplastic disorders, such as neuropsychiatric disorders, pulmonary disease, and several kinds of infections, including HIV infection (7, 12, 18, 31, 33). A significant correlation was observed between SIADH and severe meningeal inflammation (27). SIADH associated with Brucella infection is rare, and it was first reported in 1988, with 14 cases documented (5). Our case of Brucella infection affecting the CNS and causing meningoencephalitis associated with SIADH is the second reported in the international literature.

The second episode of endocrine and metabolic disorder was the spontaneous development of water diuresis, consistent with a diagnosis of central DI in all but one feature: hyponatremia. The clinical picture of the patient was further complicated by an additional endocrine deficiency, hypothyroidism, which could explain the uncharacteristic presence of hyponatremia mentioned above.

Infections of the CNS are a known potential cause of hypothalamic and/or pituitary dysfunction. Reports on this phenomenon, however, are relatively rare, as are systematic studies of the matter. In most case reports, the reduction in hormone secretion had been caused by infectious agents (13, 19, 21, 24, 35), especially Mycobacterium tuberculosis (30). To the best of our knowledge, only two cases of DI in association with neurobrucellosis have been published in the literature, one reported over 40 years ago (14) and another in 2000 (34). Our report presents a rare case of neurobrucellosis causing SIADH, leading in turn to DI and hypothyroidism with hypnatremia. As far as we know, such a case has never been reported before.

Although neurological involvement of the CNS is rare in patients affected by brucellosis, several well-documented cases are available in the literature (1, 8, 15, 17, 34, 36). Nevertheless, the case reported here is unique due to the concomitant presence of SIADH, DI, and hypothyroidism as consequences of Brucella infection.

In conclusion, our case provides evidence of metabolic and endocrine disorders following Brucella infection of the CNS. Neurobrucellosis, although rare, should be considered in cases of neurological disease of unknown etiology, especially in patients from endemic areas. The exact clinical manifestations and complications of neurobrucellosis have not been fully determined as yet, and further studies are required to elucidate this clinical heterogeneity. Through earlier diagnoses and more appropriate antibiotic treatment, such information would allow the prevention of neurological as well as endocrine sequelae. Hypothalamic and/or pituitary function should be monitored in patients infected with Brucella species to ensure the immediate treatment of any complications.

REFERENCES


