Neuroleptospirosis: unexplored & overlooked

Leptospirosis is caused by pathogenic spirochetes of the genus *Leptospira* and remains a challenge for public health officials and researchers, presenting significantly high rates of morbidity and mortality. The leptospires are typically transmitted through direct or indirect contact with the urine of an infected animal. It is the most widespread zoonosis in the world and is associated with a constellation of pathophysiological phenomena in human hosts: sepsis, acute renal failure, hepatic dysfunction, electrolyte imbalance, pulmonary haemorrhage, cardiovascular collapse, thrombocytopenia, pancreatitis, myocarditis, rhabdomyolysis, acalculous cholecystitis, purpuric skin lesions, pericarditis, and arthritis. The more severe form of the disease is known as Weil’s disease. In Brazil, human leptospirosis is also an endemic malady presenting a cyclic pattern, the majority of cases occurring during the rainy season in both urban and rural environments. At the Emílio Ribas Institute of Infectology, Sao Paulo, the annual incidence of leptospirosis is approximately 50 confirmed cases and 100 suspected cases, together representing 8 per cent of admissions to the intensive care unit. We also have observed cases of neuroleptospirosis, as illustrated in our previous reports.

In classical icteric leptospirosis (Weil’s disease), as well as in anicteric leptospirosis, involvement of the central nervous system is well documented, affecting children and adults alike, and can present as any of the following phenomena: cerebrovascular accident, cerebral venous thrombosis, cerebral arteritis, subarachnoid haemorrhage, blindness due to uveitis, optic neuritis, transverse myelitis, cranial nerve palsy, Guillain-Barré syndrome, mononeuritis multiplex, peripheral nerve palsy, psychosis, suicidal behaviour, cerebellitis, encephalitis, meningitis, chronic meningitis, and primary meningitis.

Meningitis can be a significant feature of the clinical profile of leptospirosis, principally in the milder, anicteric forms of the disease. Meningeal involvement in leptospirosis is typically biphasic in nature. The early phase is the septic phase, during which non-specific symptoms, such as viral illness are seen. The later phase is the immunological phase, in which the clinical manifestations of meningitis are classic. During the septic phase, leptospires can be recovered from the cerebrospinal fluid (CSF) by culture or by polymerase chain reaction (PCR). During the immunological phase, lymphocytic pleocytosis occurs, with total cell counts usually below 500/µl, and the diagnosis can be made through immunological tests. In that later phase, the CSF is characterized by protein levels between 50 and 300 mg/dl, and the glucose concentration is generally normal. Leptospiral meningitis accounts for 5 to 40 per cent of all cases of aseptic meningitis, depending on the method of detection, and is characterized by a greater incidence in children than in adults. In addition, the incidence of abnormal CSF in adult patients with Weil’s disease is as high as 100 per cent. In a retrospective study of 43 consecutive urban-dwelling children (35 boys and 8 girls, 4-14 yr of age) presenting leptospirosis, meningitis was diagnosed in 10 cases (23%). It is noteworthy that 10 per cent of the cases of leptospirosis appear as an acute meningeal syndrome without any other apparent foci. The use of PCR can facilitate the diagnosis, principally during the septic phase of
disease, when the antibodies are absent or at low levels, and leptospires are observed in high numbers in the serum as well as in the CSF. The number of diagnosed cases of leptospirosis involving aseptic meningitis has increased considerably since new and powerful diagnostic tools, such as PCR, have been employed, and since clinical suspicion of the disease has been heightened. Interestingly, the infectious agent isolated by Tatlock in 1944 and maintained by serial animal passages, was believed to be a virus until 1952, when Gochenour et al identified the agent as a leptospire.

Leptospiral meningitis was first described by Laubry and Parvu in 1910. In 1965, Heath et al stated that anicteric leptospirosis has directed the attention of investigators to the possible leptospiral aetiology of previous episodes of undiagnosed human illness. Nevertheless, the classical icteric profile resulting from leptospirosis continues to captivate the minds of physicians. Therefore, primary central nervous system involvement in leptospirosis has been overlooked and underreported. In fact, this misunderstanding of the true nature of leptospirosis has had significant consequences on the diagnosis and prompt treatment of the disease. Several additional factors might contribute to the under-diagnosis of neuroleptospirosis. First, it can be misdiagnosed as other diseases such as aseptic viral meningitis. In addition, appropriate diagnostic tools such as sensitive, fast, and specific assays, are not available at most facilities. Further, serological and immunological tests are occasionally performed at the early stages of the disease, when the antibodies are absent. Finally, the indiscriminate use of antibiotics has decreased the likelihood of obtaining an isolate.

Leptospirosis is usually an acute disease, although leptospires can survive the immune defences and persist in places such as the proximal renal tubule, aqueous humor, and subarachnoid space, resulting in chronic disease, manifesting, respectively, as nephritis, uveitis, and chronic meningitis, the last being rare or underdiagnosed. In 1937, Murgatroyd reported an unusual case of chronic meningitis in a patient who failed to recover completely from Weil’s disease. The interesting feature of the case concerns the late onset of the symptoms of meningeal inflammation and the isolation of leptospires from CSF and urine at 25 and 35 wk, respectively, from the onset of the illness, as determined by guinea pig inoculation. It is likely that chronic meningitis resulted from gradual proliferation of leptospires in the subarachnoid space of a patient who had an immunological deficiency, as evidenced by the absence of agglutination for the specific organism in the patient serum. The only other recorded case bearing any resemblance to this is one reported by Davidson and Smith in 1936, who investigated an outbreak of Weil’s disease in Aberdeen, Scotland. Therefore, leptospiral meningitis has been reported in various presentations: primary or isolated meningitis, characterized by focal aseptic meningitis without any other foci of leptospiral infection; chronic meningitis, characterized by isolation of leptospires in cerebrospinal fluid and late onset of symptoms; and the classic immunological meningitis, characterized by systemic disease accompanied by aseptic meningitis. These three forms of leptospiral meningitis are usually associated with the Leptospira interrogans serovars icterohaemorrhagiae, copenhageni, canicola, and pomona.

One of the most intriguing aspects of leptospiral infection is the lack of knowledge regarding the mechanisms involved in its neurological spectrum. The remarkable discovery of the cytokine network link to pathophysiology of bacterial meningitis and the expansion of studies into the cell adhesion process have increased our knowledge of the inflammatory response within the subarachnoid space as well as of bacterial cell interaction. Therefore, by analogy to the known mechanisms of bacterial meningitis, we can pose some questions regarding human neuroleptospirosis. Are cytokines, chemokines, reactive oxygen species, reactive nitrogen species and other inflammatory mediators involved in meningitis and the various neurological events secondary to
leptospirosis? What is the cytokine pattern? How do leptospires cross the blood-brain barrier (BBB)? Does such leptospiral trafficking involve an intercellular or intracellular pathway?

It is well known that virulent leptospires can gain access to the bloodstream through the skin or mucosa. After invading the bloodstream, leptospires play a role in the activation of innate immunity cells, such as macrophages, via interaction among the transmembrane toll-like receptor 2 (TLR2), CD14, and leptospiral lipopolysaccharide. In order to migrate from the bloodstream to the CSF, the microorganisms must cross the BBB. However, there are some pathophysiological features that have not yet been explored. Such features include leptospiral neurotropism and the capacity of leptospires to invade human brain meninges. To move from the environment into the subarachnoid space, the pathogenic leptospires must succeed in crossing the cutaneous tissue or mucosa and, subsequently, the BBB. Although leptospires can be seen within and attached to endothelial and conjunctival cells, the molecular mechanisms by which these spirochetes interact with both cellular barriers, as well as the chain of events involved in leptospiral meningitis and other leptospirosis-related neurological phenomena, remain unknown.

Another enigmatic facet of neuroleptospirosis is related to neuropsychiatric disorders, such as delirium, hallucinations, psychosis, mania, and even suicidal behaviour, which often appear during the early phase of leptospirosis in the absence of renal or hepatic dysfunction. Therefore, it is unlikely that these behavioural disorders are attributable to uraemia or hyperbilirubinaemia.

In this issue, Mathew et al. have highlighted the pathological, clinical, and laboratory features of neuroleptospirosis patients treated at their institution and have proposed two indicators of poor prognosis: significant deterioration in mental status and elevated CSF protein at admission. The authors are indeed correct to affirm that “icterus and conjunctival changes are not universal and their absence should not be taken as evidence against the diagnosis of leptospiral infection”. Without a doubt, neuroleptospirosis can be the primary manifestation of leptospirosis. Karande et al. reported the case of a 10 yr old male leptospirosis patient presenting meningitis accompanied by normal liver and kidney function. It is also worthy of mention that leptospirosis can manifest as acute renal failure without jaundice or hyperbilirubinaemia. We recently reported the case of a 19 month old male child presenting meningitis and acute renal failure without icterus, which is uncommon and made the diagnosis more difficult. In order to detect and encompass the unusual forms of leptospirosis and cases of neuroleptospirosis, a preliminary diagnosis should be hypothesised based on epidemiological clues and not only on the typical findings of leptospirosis.

In conclusion, although leptospirosis has been implicated in various neurological disturbances, it has typically been overlooked and unexplored as a potential aetiological factor in such disturbances. One of the most promising advances is the discovery of leptospiral genes that are potentially related to the mechanisms of motility, chemotaxis, adhesion, invasion, lipopolysaccharide biosynthesis, and loss of endothelial homeostasis, as well as that of hemostasis in human host. This knowledge of the genome could expand our understanding and provide new clues as to the pathogenesis of leptospirosis and its neurological phenomena.

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