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A 16 Year-Old Girl with Fever, Abdominal Pain and Progressive Neurological Deficits

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Abstract

Introduction: Listeria monocytogenes is a small gram positive bacillus that can be isolated from soil, vegetation or animal reservoirs. Human disease occurs mainly in immunocompromised people, neonates and in pregnancy while the cases in immunocompetent people are rare. CNS manifestations of the disease can be in form of meningitis, encephalitis and also cerebritis since L. monocytogenes shows tropism for brain and brain stem as well for the meninges.

Case presentation: A 16 year-old girl, who had been previously healthy, came at our attention because of progressive neurological deficits. The symptoms of the disease were present two months before the admission when she had experienced intermittent and severe headaches and fever up to 38 C, nausea, vomiting and abdominal pain lasting for 5 days. Her symptoms included lethargy and pain at the moment of admission.

After having developed diplopia and unsteady gait after three weeks she was admitted in our department. Multiple cranial neuropathies were present. Neurological diagnosis was rhombencephalitis. CSF analysis showed a colorless fluid, 10 lymphocytes/mm3, 77 mg/dl protein, and 69 mg/dl glucose.

Serum samples obtained during the admission were positive for Listeria and she was treated with ampicillin and gentamicine accordingly, with a good immediate response.

Conclusion: The most important feature of this paper is its extended differential diagnosis comprising tumoral, inflammatory, vascuar and infectious diseases. Thus, it represents a valuable aid for all concerned specialist of above-mentioned fields.

Keywords: pontine lesion, rhombencephalitis, MRI, Listeria monocytogenes.

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CASE PRESENTATION

A16 year-old girl, in previously excellent health status, resident in the rural periphery of Prishtina (Kosova) was admitted at our department because of progressive neurological deficits.

Approximately 2 months before this admission, she began to have intermittent and severe headaches and fever up to 38 C, nausea, vomiting and abdominal pain lasting for 5 days. She was admitted at that time to the emergency service of the local hospital.

During admission at the above mentioned hospital her symptoms included lethargy and pain. Her temperature was 37.9°C, and her pulse 112 beats per minute; respirations were 20 breaths per minute, and the oxygen saturation was 95% while the patient was breathing ambient air. Her pupils were equal and reactive to light and accommodation. Mucous membranes were dry and pink. The neck was moderately rigid.

Question for consideration: Discuss on the principal syndromes towards this clinical picture.

COMPLEMENTARY EXAMS

Numerous causes, ranging from acute life-threatening emergencies to chronic functional disease and disorders of several organ systems can generate abdominal pain, fever and suddenly headaches. Among the most common causes, the following can be listed:

- gastro-enteritis (inflammatory disease, bacterial or viral infection, obstruction)
- meningitis (nuchal rigidity, headache, photophobia, and prostration; may not be febrile)
- intracranial especially subarachnoidal hemorrhage (nuchal rigidity and headache; may not induce clouded consciousness or seizures. Hemorrhage may not be seen on CT scan. Lumbar puncture shows “bloody tap” that does not clear by the last tube.

Complete neurological exam is an essential first step. If this exam is abnormal or if it is serious underlying cause is suspected for any reason and as a result an imaging study (CT or MRI) is indicated.

A computed tomographic (CT) scanning of brain was performed showing no abnormality. The cerebrospinal fluid (CSF) was non-hemorrhagic. Biochemical exam showed three red blood cells/mm3, 70 white blood cells/mm3 (63% neutrophils and 37% mononuclear cells), a protein and glucose level of 40 mg/dl and 63 mg/dl respectively. Results of routine hematologic tests; tests of coagulation, renal function, and liver function; the level of C-reactive protein; electrolyte levels; and a toxicology screen were normal.

Since the abdominal pain and vomiting persisted, a fibrogastroscopy was performed; The final diagnosis was given:‘acute gastrointestinal infection’ and a symptomatic treatment was prescribed.

Three weeks after, the patient developed diplopia and unsteady gait and she was admitted at our department. Multiple cranial neuropathies were present: bilateral internuclearopthalmo-plegia, horizontal and vertical nystagmus, right trigeminal palsy (right hemi-facial hypoesthesia, direct and consensual corneal hyporeflexia, oblique mouth) right peripheral facial palsy (grade III according House Brachman), mixed nerve palsy (fausse-routes), vertigo and static and dynamic ataxia.

Question for consideration: From semiology to topography, where it may be the lesion location?

NEUROLOGICAL REASONING AND TREATMENT

A brainstem syndrome is clinically suspected when the patient presents diplopia, ataxia, disturbance of consciousness. By means of the Rostro-caudal plan, the lesions are categorized as:

1) **Rostral medulla**: massive bulging of the dorso-lateral area due to the restiform body;

2) **Middle medulla**: bulging of the lateral surface due to the inferior olive;

3) **Caudal medulla**: relatively round shape without bulging of the lateral surface.

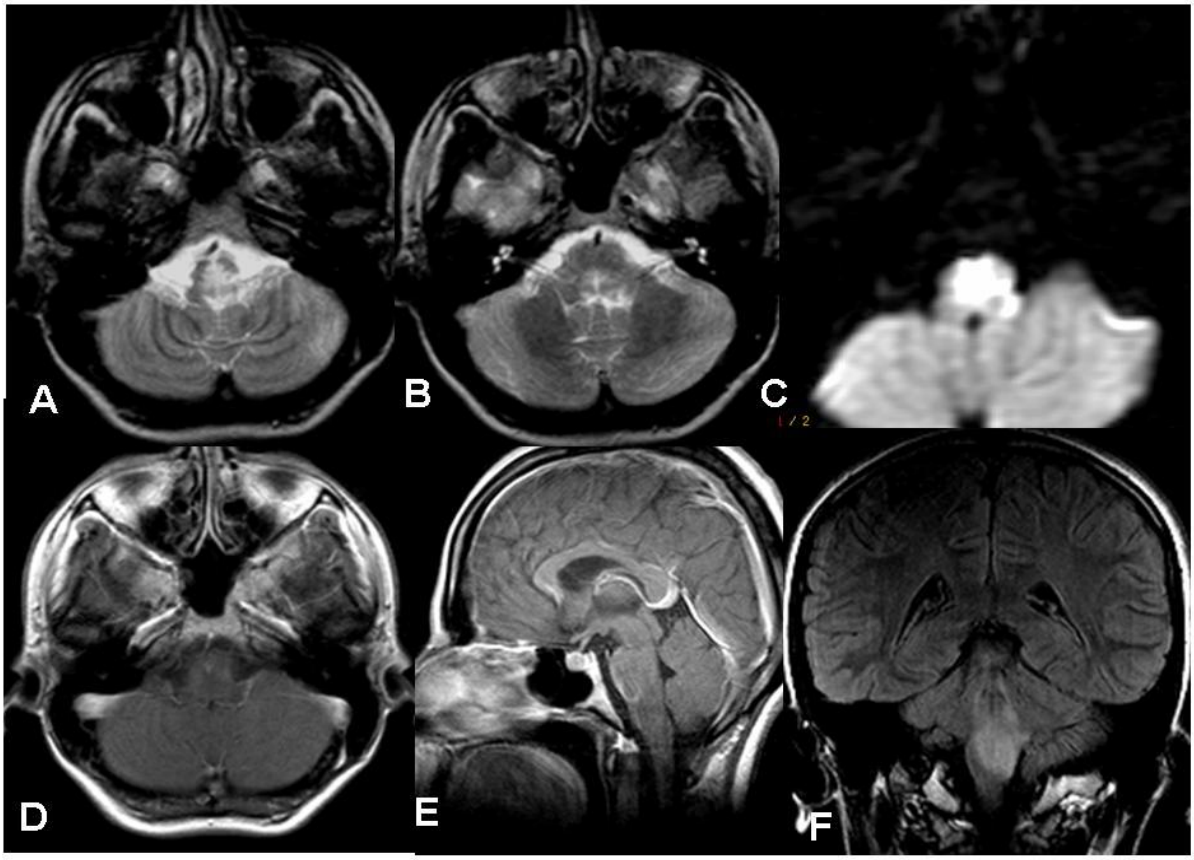
Clinically, the patients of the rostral group usually present dysphagia, dysarthria, facial paresis and a bilateral trigeminal sensory pattern significantly more often severe than caudal group patients; whereas gait ataxia, headache, isolated limb/body sensory pattern and sensory gradient worse in the leg than in the arm are significantly less often than caudal group patients.

Using horizontally axes, the classification is as follows: 1) **Typical type**: Diagonal band-shaped lesions sparing the most dorso-lateral portion, most common; 2) **Ventral type**: Similarly shaped, but more ventrally situated lesions involving some portion of the inferior olive and sparing relatively large portions of the dorso-lateral area; 3) **Large type**: Large lesions extending ventrally so as to involve some portion of the olivary nucleus and dorsally to involve most of the dorso-lateral area; 4) **Dorsal type**: Lesions restricted to the most dorsal or dorso-lateral portion; 5) **Lateral type**: Some lesions were restricted to the lateral, superficial area without extending dorsally; 6) **Unclassifiable type**: Other lesions not classifiable.

Clinically, the frequencies of dysphagia, dysarthria, Horner sign and bilateral trigeminal sensory pattern are significantly different among horizontal subtypes: ‘large type’ lesions tended to have frequent dysphagia, hoarseness, dysarthria and bilateral trigeminal sensory pattern. These symptoms were uncommon in those with lateral lesions. Horner sign tended to be uncommon in pts with dorsal lesions.

Cerebral magnetic resonance imaging (MRI) showed an increased T2-weighted signal associated with restricted diffusion involving the brainstem, the left middle cerebellar peduncle and cervico-medullary junction which was interpreted as a demyelization process (Fig. 1).

Fig. 1. Cerebral MRI at admission. Hypersignal in cervico-medullary junction at axial T2-weighted (A and B) as well as Flair (F) with homogeneous restriction in DWI (C) and scant contrast enhancement in axial (D) and sagital (E) scans.



Subsequently, the patient received a 3-day treatment of Methylprednisolone sodium succinate (Solu-Medrol) (1g/day). Since the clinical status of our patient deteriorated, thus she was admitted at our department.

Questions for consideration:

- discuss on the radiological differential diagnosis of this lesion.
- which complementary diagnostic test would you recommend?

DISCUSSION AND FINAL DIAGNOSIS

The radiological findings at this case are compatible with rhombencephalitis.

Rhombencephalitis is serious, uncommon illness originally described by Bickerstaff and Cloake (1), which is very difficult to diagnose clinically. Patients typically present with symptoms of areflexia, ataxia, and ophthalmoplegia (1).

The etiology is frequently undetermined; there are many inflammatory, vascular, neoplastic, metabolic and demyelination conditions which

show radiological features similar to those of our patient on magnetic resonance imaging (MRI).

Acomplete and exhaustive laboratory work-up was performed: white-cell count of 26,200 cells per mm3 (84.8%-neutrophils), eritrose-dimentation rate of 30mm/h, C-reactive protein of 4mg/dl. The rest of tests (renal and liver function, electrolytes) was normal. Routine cerebrospinal fluid (CSF) exam showed a colorless fluid, 10 lymphocytes/mm3, 77 mg/dl protein, and 69 mg/dl glucose. Cultures of the cerebrospinal fluid and blood testing for infectious agents (including cytomegalovirus, Epstein–Barr virus, herpes simplex virus [HSV] type 1 and type 2 and for Lyme, lysteria monocytogenes and syphilis were negative. Tests for angiotensine-converting enzyme and antinuclear antibodies were negative on blood and CSF. CSF PCR for Whipple disease was negative as well.

Cerebrovascular Disease

The progressive development of neurological disorders and the young age of our patient make this diagnosis unlikely. In this patient, the results of magnetic resonance angiography ruled out vascular occlusion and the cerebrospinal fluid findings suggested causes other than stroke.

Central Pontine Myelinolysis (CPM)

It constitutes the major risk of developing cerebral demyelinating lesions as a result of a rapid correction of a chronic hyponatremia. Given the fact that our patient did not present hyponatremia and the MRI lesion lacked the characteristics of CPM (triangular lesion located ventrally in the basis of pontis with sparing of tegmentum and corticobulbar tracts), this diagnosis seemed less probable.

Demyelization Disorders

The patient was treated with corticosteroids, probably because a demyelinating disorder was considered. However, this 16-year-old girl had no history of visual or neurologic deficits. The findings of MRI lacked the characteristics of demyelinating process. The absence of oligoclonal band on CSF and of a clinical response to corticosteroids does not also support the diagnosis of multiple sclerosis.

Neuro-sarcoidosis

Sarcoidosis can affect the CNS with basal meningitis and cranial neuropathies. Parenchymal lesions preferentially occur in the brain stem and hypothalamus (2). However, the symptoms of sarcoidosis are not as acute as those in this patient and the cranial nerves, The normal level of angiotensin-converting enzyme in the cerebrospinal fluid and the absence of pulmonary manifestations argued against the diagnosis of sarcoidosis (3).

CNS Whipple disease (WD)

Among the systemic manifestations of WD, our patient presented with abdominal pain and fever and lacked chronic migratory arthralgias or polyarthralgias (which for several years precede the onset of neurological symptoms) and unexplained weight loss. However, 4-6% of patients with CNS-WD had no systemic symptoms or signs (4). The absence of PCR in CSF makes inconclusive this diagnosis.

Inflammatory Diseases

Systemic lupus erythematosus (SLE) commonly has systemic manifestations, including the skin, joints and kidneys (5).

Neurologic manifestations include psychiatric or behavioral changes, seizures, and peripheral neuropathy; however, the clinical picture and the negative antibody testing and the oral and genital ulcers in this case rule out a diagnosis of SLE. Basal meningitis can occur in Wegener's granulomatosis, causing cranial neuropathies, headaches, strokes and seizures. The cerebrospinal fluid profile shows a mild-to-moderate lymphocytic pleocytosis and increased total protein and IgG index. The antineutrophil cytoplasmic antibodies in our case was negative, as well as the lack of pulmonary, sinus, or renal involvement, Wegener's granulomatosis was unlikely (6).

Neuro-Behçet's Disease

In addition to oral and genital ulcers, uveitis, skin lesions, arthritis, thrombophlebitis, a positive family history, and gastrointestinal, CNS, or vascular involvement are common features of the disease (7, 8). The absence of any of these manifestations as well as lack of improvement after corticotherapy ruled out this hypothesis.

Infectious Diseases

HSV encephalitis has a predilection for the temporal lobes and may be necrotizing and hemorrhagic (9). The most important, PCR testing for HSV DNA, a highly sensitive and specific assay was negative, making this diagnosis highly unlikely.

Meningovascular syphilis may occur within the first 12 months after primary infection and is associated with headache and meningismus (see Figs 6 and 8, page 257 of Greenfield's Neuropathology (10). It produces a basal meningitis, and cranial-nerve palsies (seventh, sixth, or second cranial nerve, in decreasing order of occurrence) are common (10). The absence of genital ulcers and the negativity of testing for syphilis make less likely this disease

Other less likely infectious possibilities include: t*uberculosis, varicella–zoster virus infection, and Lyme disease*. Serologic testing for Lyme disease and Varicella–zoster virus were negative. *Listeria monocytogenes* is an uncommon etiologic agent of infection in general population. However, being an important cause of severe infections in neonates, pregnant women, the elderly and other individuals with impaired cell-mediated immunity (11). Several clinical syndromes related to Listeria infection have been described, like gastroenterocolitis, sepsis, endocarditis, central nervous system (CNS) infections, etc. CNS disease caused by Listeria includes meningitis, diffuse encephalitis and well-localized abscesses (11).

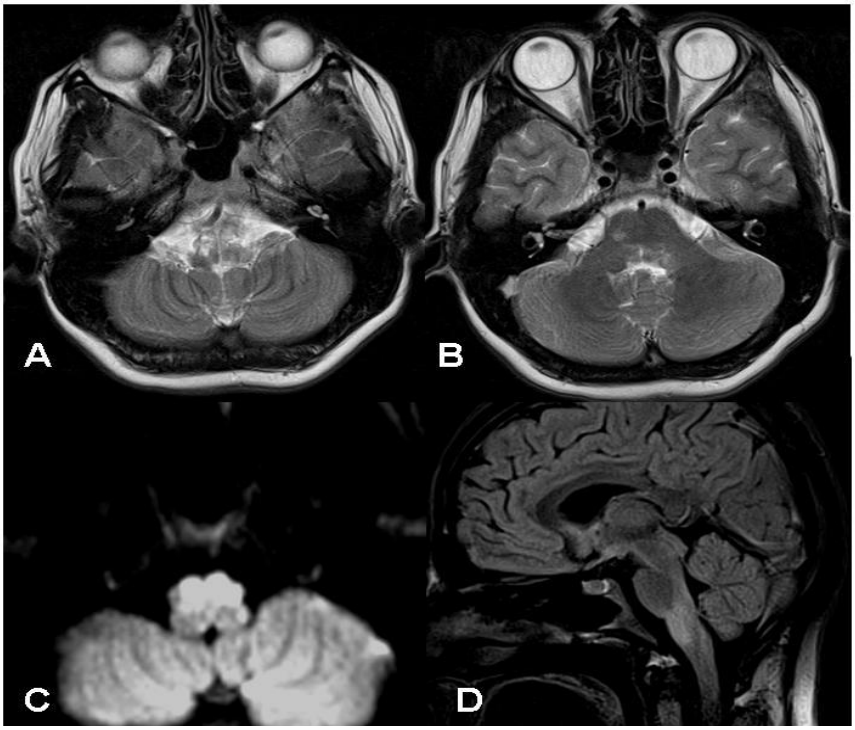
Listeria rhombencephalitis is a rare and potentially life-threatening infection. The brainstem predilection mechanism remains unexplained adequately.

Majority of cases reported are sporadic, occurring in previously healthy individuals (12). The clinical course is usually biphasic, with unspecific symptoms consisting of headache, malaise, nausea, vomiting, fever in the first 4–10 days, followed by progressive brainstem dysfunction with cranial nerves palsy, cerebellar signs, hemi- or tetraparesis, sensory deficits, respiratory insufficiency, impairment of consciousness and sometimes seizures. Initial CT of the brain usually remains normal and the MRI shows hyperintense, patchy lesions within the brainstem and/or multiple microabscesses (12). However, isolated midbrain localization was rare (3%). Meningeal signs were present in 48% of cases.

Typical markers of inflammatory response, like elevation of CRP and leucocytosis, increased percentage of immature granulocytes are usually absent. This can be explained by mainly intracellular spread of Listeria (13).

Interestingly, CSF often remains sterile with only mild, unspecific abnormalities (14). Low-grade pleocytosis (mean, 392 cells/mm3), usually with lymphocytic predominance, and low-level hyperproteinorrachia (mean, 99 mg/dL) occurred in 88% and 89% of cases, respectively, and hypoglycorrhachia occurred in 21% (1, 11, 14). Gram stains of CSF resulted positive in 14% of cases, as opposed to 28% in listerial meningitis and 60% in other bacterial meningitides.

Fig. 2. Cerebral MRI one after the onset of treatment revealing an attenuation of hypersignal in axial T2-weighted (A and B) and in sagital Flair (D) as well as diminuation of the zone with diffusion restriction (C).



CSF cultures were positive in 42% of cases, as opposed to 90% in listerial meningitis (15), most often late after admission.

Our patient's presentation at the age of 16 was more consistent with Behçet's disease; serum samples obtained on admission were positive for Listeria and she was treated with ampicillin and gentamicine accordingly with a good immediate response (Figure 2).

Successive MRI showed the quasi complete disappearance of the lesion (Figure 3).

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Not available

Specific author contribution at the study:

E.R. (concept, design, data collection, writing, reviewing, final approval)

A.R. (data collection, analysis, drafting, reviewing, final approval)

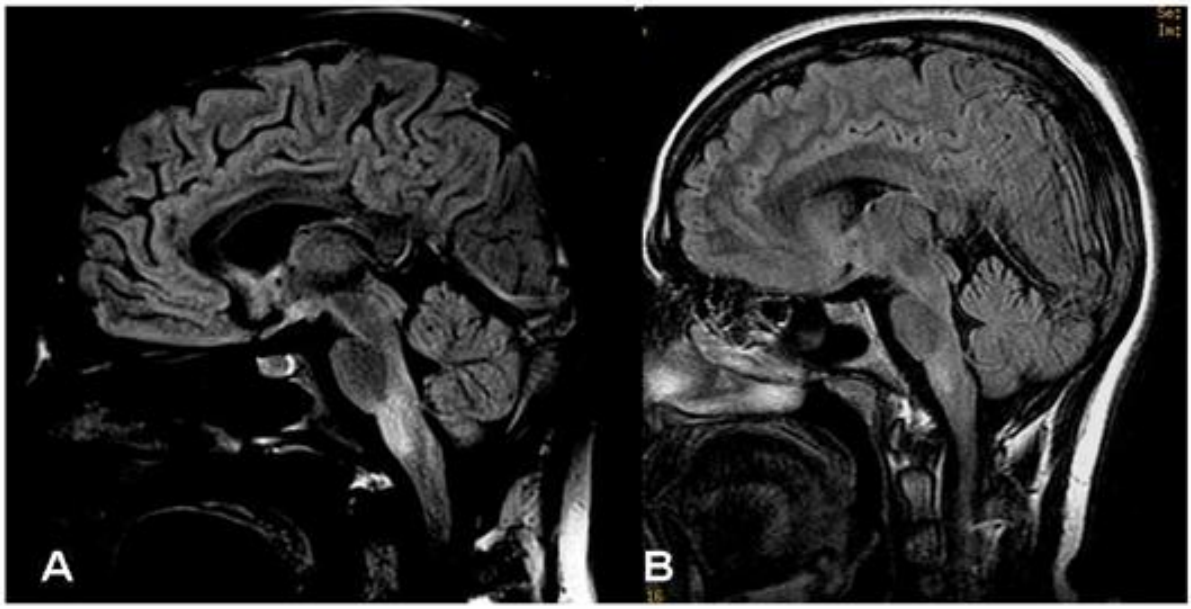

Figure 3. Net radiological response comparing the MRI of one month after the treatment (A) with that at 1 year of follow-up (B).

This case underscores that Listerial rhomboencephalitis is a syndrome observed predominantly in previously healthy adults without history of immunosuppression and emphasizes also the utility of a wide differential diagnosis.

M.P. (data analysis, differential diagnosis, drafting, reviewing, final approval)

G.K. (concept, design, data collection, writing, reviewing, final approval)

REFERENCES

1. Armstrong R.W, a Fung P.C. Brainstem encephalitis (rhomboencephalitis) due to Listeria monocytogenes: case report and review*Clinical Infectious Disease* 1993;16:689-702.
2. Bihan H, Christozova V, Dumas JL, Jomaa R, Valeyre D, Tazi A, Reach G, Krivitzky A,Cohen R. Sarcoidosis: clinical, hormonal, and magnetic resonance imaging (MRI) manifestations of hypothalamic-pituitary disease in 9 patients and review of the literature. *Medicine Baltimore* 2007;86(5):259-68.
3. Sharma OP. Neurosarcoidosis: a personal perspective based on the study of 37 patients. *Chest* 1997;112:220-8.
4. Louis ED, Lynch T, Kaufmann P, Fahn S, Odel. Diagnostic guidelines in central nervous system Whipple's disease *J Ann Neurol* 1996;40(4):561-8.
5. Hiraki LT, Benseler SM, Tyrrell PN, Hebert D, Harvey E, Silverman ED. Clinical and laboratory characteristics and long-term outcome of pediatric systemic lupus erythematosus: A longitudinal study *J Pediatr* 2008;152(4):550-6.
6. Spranger M, Schwab S, Meinck HMTischendorf M, Sis J, Breitbart A, Andrassy K. Meningeal involvement in Wegener's granulomatosis confirmed and monitored by positive circulating antineutrophil cytoplasm in cerebrospinal fluid *Neurology* 1997;48(1):263-5.
7. Bang DS, Oh SH, Lee KH, Lee ES, Lee SN. Influence of sex on patients with Behçet's disease in Korea *J Korean Med* Sci 2003;18:231-5.
8. Deuter CM, Kötter I, Wallace GR, Murray PI, Stübiger N, Zierhut M. Behçet's disease: Ocular effects and treatment *ProgRetin Eye Res* 2008;27:111-36.
9. Hindmarsh T, Lindqvist M, Olding-Stenkvist E, Sköldenberg B, Forsgren M. Accuracy of computed tomography in the diagnosis of herpes simplex encephalitis *ActaRadiolSuppl* 1986;369:192-6.
10. Tyler KL, Sandberg E, Baum KF. Medical medullary syndrome and meningovascular syphilis: a case report in an HIV-infected man and a review of the literature *Neurology* 1994;44(12):2231-5.
11. Drevets DA, Bronze MS. Listeria monocytogenes: epidemiology, human disease, and mechanisms of brain invasion *FEMSImmunol Med Microbiol* 2008 Jul; 53(2):151-65.
12. Mrowka M, Graf L-P, Odin P. MRI findings in mesenrhombencephalitis due to Listeria monocytogenes *J NeurolNeurosurg Psychiatry* 2002;73(6):775-77.
13. Antal EA, Løberg EM, Bracht P, Melby KK, Maehlen J. Evidence for intraaxonal spread of Listeria monocytogenes from the periphery to the central nervous system*Brain Pathol* 2001;11:432–8.
14. Bartt R. Listeria and atypical presentations of Listeria in the central nervous system *Seminars in Neurology*2000;20(3):361–73.
15. Paul MLDwyer DE, Chow C, Robson J, Chambers I, Eagles G.Listeriosis: a review of eighty-four cases *Med. J. Aust* 1994;160(8):489-93.