Ophelia Syndrome: Hodgkin Lymphoma with Limbic Encephalitis

MONICA JUNEJA, SATNAM KAUR, DEVENDRA MISHRA AND *SILKY JAIN

*From Department of Pediatrics, Maulana Azad Medical College and associated Lok Nayak hospital; and *Department of Pediatric Hemato-Oncology, Rajiv Gandhi Cancer Institute and Research Centre, Rohini; New Delhi, India.*

Correspondence to:
Dr Satnam Kaur, Assistant Professor, Department of Pediatrics, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi 110 002, India.
sk_doc@yahoo.co.in
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Background: Limbic encephalitis, an immune-mediated encephalitis, results from inflammation in the medial temporal lobes. The paraneoplastic form is rare in pediatric population, and frequently precedes tumor diagnosis. **Case characteristics**: A 9-year-old boy receiving chemotherapy for Hodgkin lymphoma, developed headache, temporal lobe seizures, anxiety, hallucinations, short-term memory loss and autonomic disturbances. Magnetic resonance imaging of brain showed features suggestive of limbic encephalitis. Electro-encephalography showed diffuse slowing with no epileptiform discharges. **Outcome**: We diagnosed paraneoplastic form of limbic encephalitis. Treatment with steroids and intravenous immunoglobulin failed, and the child died 4 weeks after onset of symptoms. **Message**: Limbic encephalitis should be kept as differential diagnosis in a child with sub-acutely evolving neuropsychiatric symptoms.

Keywords: *Lymphoma, Magnetic resonance Imaging, Paraneoplastic syndrome.*

Limbic encephalitis is a neurological syndrome resulting from inflammatory lesions in the medial temporal lobes [1]. It typically presents with subacute onset of short term memory deficits, temporal lobe seizures, mood/sleep disturbances and hallucinations, and may progress to dementia [1]. Paraneoplastic form of limbic encephalitis is rare in children, but is being increasingly recognized [1]. We report a child with Hodgkin lymphoma who developed limbic encephalitis while undergoing chemotherapy.

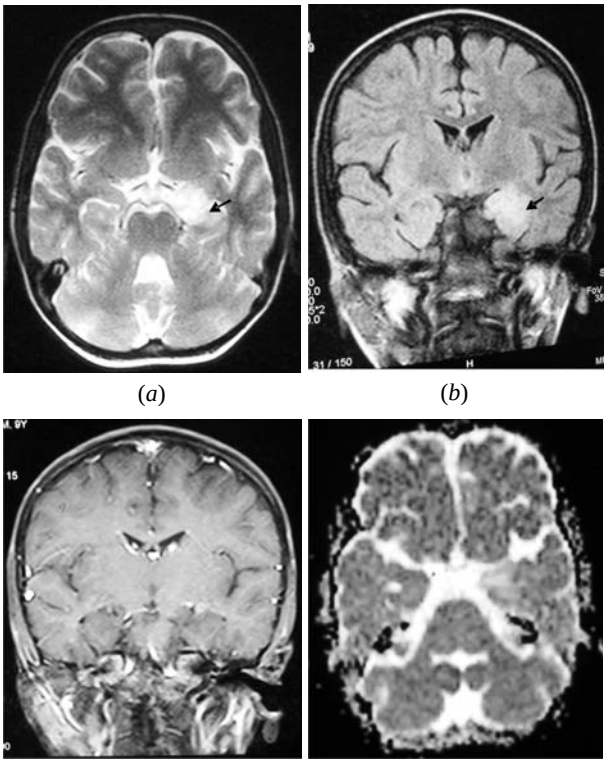
CASE REPORT

A 9-year-old boy, diagnosed as Hodgkin lymphoma (mixed cellularity type) three months ago, was admitted for third cycle of chemotherapy (Adriamycin, Bleomycin, Vinblastine, Dacarbazine). At admission, he complained of mild, diffuse headache persisting for last 10-12 days. There was no altered sensorium, seizures, focal neurological deficits or any history suggestive of raised intracranial pressure. The neurological examination and the fundus evaluation were normal. Two days later, he developed multiple episodes of complex partial seizures starting with oromotor sensory symptoms. On the same day, child complained of difficulty in walking; and on examination was found to have weakness of the hamstrings on the right side along with bilateral brisk tendon reflexes and extensor plantar response. Magnetic resonance imaging (MRI) done on the same day was normal. Cerebrospinal fluid (CSF) examination showed normal biochemistry, no malignant cells, and negative herpes simplex virus (HSV) serology. Elecgro-encephaloography (EEG) was within normal limits. Over the next four days, the child was noted to have decreased spontaneous activity, overall reduced interaction and decreased speech. There were long periods of anxiety with insomnia along with visual hallucinations.

Over next few days, symptoms evolved to short-term memory loss with intact long-term memory. Repeat MRI showed features suggestive of limbic encephalitis (***Fig.* 1**). Repeat EEG showed diffuse slowing with no epileptiform discharges. Repeat CSF study was normal; examination for oligoclonal bands in CSF could not be done. Anti-NMDA antibodies in serum were negative. Other neuronal autoantibody tests, including onconeural antibodies, could not be done. Injection methylprednisolone (30 mg/kg/day) was started for management of limbic encephalitis. Subsequently, the child completed a course of intravenous immunoglobulins (IVIG), but continued to deteriorate with progression of weakness to all four limbs, cranial nerve involvement, rhythmic movement disorder involving right upper limb, and autonomic dysfunction. He died four weeks after the onset of symptoms.

DISCUSSION

Paraneoplastic neurological syndromes are rare complications of Hodgkin lymphoma [2]. Of all these, cerebellar degeneration and limbic encephalitis are well-characterized. Association of limbic encephalitis with Hodgkin lymphoma has also been termed as Ophelia syndrome. The diagnostic criteria of paraneoplastic limbic encephalitis formulated by Paraneoplastic Neurological Syndromes Euronetwork [3] include: (*i*) subacute onset (days or up to 12 weeks) of seizures, short-term memory loss, confusion and psychiatric symptoms; (*ii*) neuropathological or neuroradiological evidence of involvement of the limbic system; (*iii*) exclusion of other possible etiologies of limbic dysfunction; and (*iv*) demonstration of a cancer within 5 years of the diagnosis of



(*a*) (*b*)

(*c*) (*d*)

FIG. 1 *MRI brain of the patient done 19 days after onset, demonstrating hyperintensities in the left hippocampus and medial temporal lobe on T2-weighted (a); and FLAIR sequences (b), with no contrast enhancement in post gadolinium images (c), suggestive of limbic encephalitis. The lesion appears bright on the ADC map (axial) (d) suggesting there is no evidence of restricted diffusion.*

the neurological disorder or demonstration of a well-characterized paraneoplastic antibody. The subacute onset of limbic encephalitis is unlike other neurological disorders in Hodgkin lymphoma, which are predominantly acute in onset [4]. Though antibody testing could not be done in our patient, he fulfilled these criteria. The main differential diagnosis of Herpes simplex encephalitis was ruled out by negative serology in our case.

The pathogenesis of limbic encephalitis involves an autoimmune process. It has been broadly categorised into two groups: associated with antibodies against intracellular neuronal antigens or with antibodies directed against cell membrane/extracellular antigens [5,6]. Whereas the first group is frequently associated with cancers (lung, testis and breast) and responds poorly to treatment, the second group is less frequently associated with cancers, and responds favourably to immunotherapy [5-7]. The majority of cases of limbic encephalitis in children are non-paraneoplastic. In a series of ten pediatric patients (<18 years) with limbic encephalitis, only one had a tumour [1]. Our case adds to the few previous reports of paraneoplastic limbic encephalitis in children [1,8].

Frequently (60%), neurological manifestations of limbic encephalitis precede tumor diagnosis [8]. In the absence of any tumor, regular evaluation for tumor occurrence should continue, especially if onconeural antibodies are detected [1]. Early immunotherapy is recommened for treatment of limbic encephalitis [9]. Intravenous immunoglobulins, steroids and plasma exchange are usual first line treatment; cyclophophamide and rituximab are used in non-responders [6,10].

We conclude that limbic encephalitis should be suspected in a child with sub-acute onset of psychiatric symptoms, with or without associated tumor. Initial neuroimaging may be normal and serial imaging may be required to detect evolving disease.

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