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Short Communication

The Risk Criteries of Central Nervous System Involvement and the Management of its Treatment in Patients with Langerhans Cell Histiocytosis

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Langerhans Cell Histiocytosis (LCH) is a rare disease of monocytic-macrophage system and it is characterized by reactive clonal proliferation and accumulation of pathologic dendritic cells. Therefore, LCH was suggested recently to be a neoplastic disease and BRAF-V600E mutation is seen 60% of patients with LCH [1]. LCH affects various organs such as bone, lungs, skin, liver, spleen, lymph nodes and Central Nervous System (CNS). LCH CNS disease can be divided into two groups. One is focal mass lesions; other is lesions associated with progressive neurodegeneration. Focal, space-occupying mass lesions are localised in meninges, choroid plexus and brain parenchyma which may contain $CD1a^+$ LCH cells, lymphocytes and macrophages with histology similar to extra cranial lesions. The most common involvement sites are the hypothalamic pituitary region which is leading to anterior and posterior pituitary involvement that results DI, growth hormone deficiency and thyroid function abnormalities [2]. The other neurological findings of LCH are progressive neurodegeneration (ND-LCH) which is characterized by progressive radio logical and clinical abnormalities. The ND-CNS-LCH occurs mostly in children, but rarely in adult LCH patients. There are two stages in ND-CNS-LCH: an early neurologically symptom-free stage characterized by MRI abnormalities alone and a second stage that includes prominent neurological symptoms [3] Typical T2-weighted MRI findings are the increased symmetrical MRI signal in the dentate nucleus of the cerebellum, basal ganglia, plexus choroideus and pons. LCH – associated abnormal clinical findings such as ataxia, tremor, abnormal cerebellar tests are characterized by absence of $CD1a^+$ histiocytes, an inflammatory collection of CD8+ lymphocytes with neuronal and axonal degeneration and extensive demyelination, Purkinje cell loss, gliosis that is explained as 'paraneo plastic phenomena' [4].

LCH patients known to have an increased risk for CNS complications have craniofacial involvement at the time of diagnosis (single skull lesions of the orbit, temporal, mastoid, sphenoid and ethmoid bones), Multi System (MS) involvements such as bone marrow, lung, liver and bone marrow involvements, children below the age of 2, carrying BRAF-V600E mutation in $CD207^+$ cells, treatment-resistant cases to prednisolone plus in blastin therapy for 6 months and those patients with multisystem disease (with or without detectable BRAF-V600E mutation) [5]. LCH spread to CNS would be hematogeneous or lymphatic routes. Sometimes, CNS manifestations occur even in the absence of detectable disease elsewhere in the body. [3] Hypothesized that probable pathogenesis of ND-LCH involved intracranial immune interactions and inflammatory mechanisms between LCH cells/T cells and microglial cells around micro vessels in the CNS which may be modulated or suppressed by Intravenous Immunoglobulins (IVIG). CNS prophylaxis should be considered for patients with LCH at high risk of CNS disease, including ND. Prophylaxis should be given at the early and subclinical stage in which time LCH cells seed in the CNS through the micro vessels or lymphoid routes [6].

CNS LCH mass lesions may be treated with curettage and multi focal lesions are treated with vinblastin/prednisolone. High risk and multisystem LCH is treated similarly, with oral 6-mercaptopurin added to high-risk therapy (Histiocyte Society LCHIII treatment protocol). LCHIII reported decreased relapse with 1 year of therapy for high risk patients compared to 6 months of therapy for low risk patients [7]. For patients with isolated skull lesions not at CNS risk sites, curettage may be sufficient therapy; otherwise systemic chemotherapy is recommended for patients with CNS risk lesions, parenchyma brain lesions and pituitary lesions [2].

The optimal treatment of patients with LCH-associated Abnormal CNS Imaging (LACI) and LCH-associated Abnormal CNS Symptoms (LACS) is not clear. [8] Suggested that 10 patients with LACS treated with all-trans retinoic acid reported stabilization of neurologic signs and MRI changes after a 1-year follow up [8]. IVIG treatment was reported to be effective when administered soon after a diagnosis of early period of ND-CNS disease. IVIG was administered for certain time period (3 years or 5 years) and treatment did not completely stop the progression of ND. It was concluded that IVIG therapy seems to be beneficial in slowing progression, even after patients developed neurologic symptoms [3]. Chemotherapy regimens have generally been ineffective for the treatment of long-standing LACS. Cladribine has been effectively used in the treatment of LCH CNS mass lesions, but there is no report of its efficacy in LACS [9]. Cytarabine has been effective for the treatment of LACS due to its ability to cross the blood-brain barrier and to accumulation in the Cerebro-Spinal Fluid (CSF). [10] Reported that the combination of vincristine, prednisone and cytarabine was effective in the treatment of patients with multisystem non-CNS LCH both at diagnosis and at relapse [10]. The combination of monthly cytarabine and IVIG, and daily dexamethasone (2 mg/m^2 with gradual taper) was reported by [11]. To be an effective treatment for a 10-year-old male child with MS-LCH. The neurophysiological symptoms of the patient were improved after 1 year of therapy and

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brain MRI showed significant improvement of the sellar, skull-base and cerebellar lesions [11].

Sixty percent of LCH cases harbor BRAF-V600E mutation and the use of BRAF inhibitors in refractory and relapsed LCH may be effective [12]. MAPK pathway inhibitors might be a promising option in patients with LACS, and prospective and comprehensive studies are warranted.

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