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Abstract
Langerhans cell histiocytosis (LCH) is a rare neoplasm that is caused by an uncontrolled proliferation of Langerhans cells. The clinical presentation of LCH is heterogeneous and can manifest as single or multiple osteolytic lesions, skin ulcerations, and involvement of single or multiple systems. Central nervous system (CNS) involvement is reported in 3.4–57% of patients with multisystem disease. In this article, we present the case of a young man with single system involvement (bone) of LCH who presented with seizures, headache, papilledema, and tinnitus. His magnetic resonance imaging (MRI) of the brain findings were reported as a normal study. The subtle signs of CNS involvement were missed by the radiologist. However, the high index of suspicion resulted in early diagnosis and treatment. The presence of empty sella turcica in neuroimaging could be the first sign of intracranial disease with chronic intracranial hypertension associated with LCH. This is especially correct if previous computed tomography (CT) scan of the brain was normal with normal appearance of the pituitary gland and the sella. Neuroimaging films should be reviewed by an expert neuroradiologist. In patients with new neurological symptoms who were diagnosed previously with LCH, intracranial disease has to be excluded. The workup in such case should include an MRI of the brain, CT of the brain and temporal bones, bone scan, cerebrospinal fluid analysis, ophthalmological assessment, and measurement of intracranial pressure. In patients with LCH who present with symptoms and signs of raised intracranial pressure, the term idiopathic intracranial hypertension should not be applied until an intracranial disease has been excluded totally.

Keywords: Langerhans Cell Histiocytosis; Central Nervous System Involvement; Neuroimaging; Intracranial Hypertension.
either granulomatous infiltration of intracranial deep brain structures or by a contagious spread of skull lesions into brain substance. The pathophysiology of CNS involvement in LCH is brain infiltration with granulomas that consist of CD1A positive Langerhans cells, macrophages, T lymphocytes, and variable numbers of multinucleated giant cells and eosinophils. In CNS granulomas, CD8+ T cells generally outnumber other types of T cells.

CNS involvement in LCH revealed three different types of lesions. These include circumscribed granuloma within the brain connective tissue spaces, granuloma within the brain connective tissue spaces with partial infiltration of the surrounding brain parenchyma, and neurodegenerative lesions affecting basal ganglia, brainstem, and cerebellum. The most common signs and symptoms are dysarthria and ataxia. Other signs and symptoms include seizures, intracranial hypertension, dysmetria, and behavioral or psychiatric problems. In this article, we present the case of a young man with single system involvement (bone) of LCH who presented with seizures, headache, papilledema, and tinnitus. His magnetic resonance imaging (MRI) of the brain findings were reported as a normal study. The subtle signs of CNS involvement were missed by the radiologist. However, the high index of suspicion resulted in early diagnosis and treatment. We also review the CNS involvement of LCH and the imaging findings.

**Case Report:**

A 28-year-old male who was previously healthy until six months prior to presentation to our neurology clinic when he developed right hip pain and difficulty walking and limping. He was thoroughly investigated and eventually diagnosed with LCH (single system involvement). Computed tomography (CT) scan, MRI, and a bone scan of the hip and pelvis showed right femur neck lesion with mild osteoblastic activity (Figure 1–3). Biopsy of the right femur lesion confirmed the pathological diagnosis of LCH (Figure 4). He was managed conservatively with no pharmacological intervention, and he did well for a period.
Resection of the localized femur lesion was established with plate and screw insertion. Six months later, he was seen by a neurologist for multiple complaints including dizziness, tinnitus, headache with features of raised intracranial pressure, and seizures (focal with/without loss of consciousness). His clinical examination at that time showed papilledema with no lateralizing signs. He was started on acetazolamide 250 mg twice daily and levetiracetam 500 mg twice daily. He also developed some neuropsychiatric manifestations including insomnia and irritability for which he was treated with zolpidem 5 mg at bedtime. CT scan of the brain was normal apart from empty sella (Figure 5). MRI of the brain was reported as a normal study. Due to the clinicoradiological discrepancy, the patient was admitted for thorough evaluation including lumbar puncture and for a multidisciplinary meeting to discuss his case in details including reviewing all imaging studies. CSF opening pressure was high at 30 cm of water with normal biochemical and hematological parameters. Upon reviewing the MRI images, there was an avid enhancement of the pituitary stalk with a slight thickening of its cranial aspect with no pituitary gland enlargement or pathological meningeal or brain parenchymal enhancement. Electroencephalogram (EEG) was done, which was abnormal with epileptiform discharges arising from the temporal lobe. The final diagnosis was LCH (multisystem disease including bone and CNS). He was started on chemotherapy according to the guidelines of the International Society of Histiocytosis (cytarabine and cladribine). He completed the first course successfully and needed a total of three courses. His symptoms improved significantly, and his fundus examination returned to normal.

Discussion:
CNS involvement in LCH has been recognized since the early reports of the disease. It has been defined as an important consequence of LCH especially for those...
with multiple bone lesions with involvement of the mastoid, temporal bones, orbits, involvement of other organ systems, and those with diabetes insipidus. These craniofacial bones are connected to the pituitary/hypothalamic region by the circumventricular organs, and it was suggested that the pathologic cells can migrate this pathway up to the pituitary, hypothalamus, cerebellum, basal ganglia, and pons.

In a study done by Grois et al. that involved 23 patients to define the range and the pathophysiology of CNS involvement by LCH, it was found that males are more prone to develop CNS disease than female (male: female ratio of 2:1). The mean interval between the initial diagnosis of LCH and the occurrence of neurological disease ranged from 5–20 years, although CNS disease was the initial manifestation of LCH in one of the patients in the study. Patients with multisystem LCH were likely to develop CNS disease. The most common clinical manifestations were ataxia and dysarthria. Seizure and intracranial hypertension were found only in patients with tumoral lesions. Some patients were completely asymptomatic (and remained so during the short period of follow up of less than 10 months) and were diagnosed based on incidental findings on imaging studies done to evaluate the cause of diabetes insipidus. This finding suggests that many cases are undiagnosed, and the actual incidence of CNS LCH might be higher than expected.

The radiologic appearance of CNS LCH varies according to the anatomic site. It is classified into four major groups according to the anatomic topography and signal intensity patterns. Group 1 includes osseous lesions in the craniofacial bones and/or skull base in the presence or absence of a soft-tissue extension. Group 2 is an intracranial and extra-axial disease in the hypothalamic-pituitary region, meninges, and other circumventricular organs. Group 3 is an intra-axial parenchymal disease in the gray matter or white matter, with a striking symmetry of the lesions and a clear predominance of a neurodegenerative pattern in the cerebellum and basal ganglia. Group 4 is localized or diffuse atrophy.

Neuroradiologic abnormalities of intracranial LCH were found to be of three basic types. Type 1 is poorly defined changes in white matter, type 2 is well-defined changes in grey matter, and type 3 is white matter and...
CNS Involvement in Langerhans Cell Histiocytosis, Hussein Algahtani, et al.

extra-parenchymal tumor masses. Other findings include infundibular enlargement, pituitary gland atrophy, and hydrocephalus. No evidence was found to suggest that one abnormality may progress to another. The imaging changes in type 1 include abnormal low signal intensity in the white matter on T1-weighted images and high signal intensity on T2-weighted images. These lesions did not exhibit contrast enhancement. The cerebellar medulla and brain stem were most commonly affected as well as cerebral white matter and basal ganglia. In most cases, the lesions were bilaterally symmetrical. The histopathologic findings of these lesions were varied. They include perivascular congestion and parenchymal infiltration by histiocytes (S100 negative and CD 68 positive). Parenchymal edema and demyelination were also found in the involved area. Xanthomata’s transformation of histiocytes was observed in areas with features suggestive of being “oldest” parts of lesions. This process was accompanied by Bergman’s gliosis in the cerebellar cortex where demyelination and gliosis, that included the presence of Rosenthal fibers, was associated with degeneration of Purkinje cells. The massive neuronal and axonal loss in the cerebellum results in atrophy of the cerebellar cortex and white matter.

Type 2 appears as well defined white and gray matter changes that manifest as small punctate regions of abnormal signal intensity images with well-demarcated edges, ranging from 0.2 to 1.4 cm in diameter with intense enhancement on contrast administration. In some patients, these lesions were found mainly in the pons and periventricular cerebral hemispheres. No biopsies were taken in this form of the disease. But they may represent small granulomas in the meninges or the Virchow Robin spaces, surrounding large arteries and veins. It is unclear whether these distended Virchow Robin spaces present perivascular granulomas or residual of cleared granulomas.

Type 3 manifests as bilateral, symmetrical extraparenchymal masses. These masses are found to be of dural-based or involving the choroid plexuses of the lateral ventricles and optic nerve sheaths. The masses were isointense to brain on T1-weighted images, hypointense on T2-weighted images with uniform contrast enhancement. The dural-based lesions appeared to involve the underlying brain. There was no evidence of involvement of overlying bones nor were skull defects present in the vicinity of the intracranial masses. These masses were associated with poorly-defined white matter changes in other areas of the brain.

Histopathologic findings of these lesions showed xanthofibroma and juvenile xanthogranuloma; xanthomatous histiocytes including Touton giant cells were aligned with bands and amorphous collections of fibrous tissue. Cells that were found in this type were a mix of histiocytes, variable numbers of T–lymphocytes, and small numbers of plasma cells. Langerhans cell granules were sought by electron microscopy in two cases, but not found, and no information on CD1A antigen was available. The neurodegenerative changes were also observed in granulomas located in extra-axial spaces such as the meninges and infundibulum. These changes may interfere with the axonal transfer of the vasopressin or hormones from the hypothalamic nuclei to the pituitary. This finding, together with direct damage of the pituitary by the granuloma itself, may explain the pathogenesis of diabetes insipidus and anterior pituitary hormone. Other classical radiologic findings in patients with CNS–LCH include cranial–facial involvement with osseous lesions in the bones of the orbits and the calvaria.

There are several potential mechanisms to account for the occurrence of inflammatory brain damage in LCH with or without raised intracranial pressure. Local production of proinflammatory cytokines by dendritic cells. These cytokines allow the recruitment of inflammatory cells from the circulation into the brain. This mechanism may explain the inflammatory component within and around LCH granulomas but not the ongoing inflammation in chronic lesions without Langerhans histiocytes. It was suggested that Langerhans histiocytes in the brain tissue partially lose their specific markers. Despite that, they are still capable of producing proinflammatory cytokines.

Another mechanism could be that LCH granulomas in the brain may stimulate an autoimmune response to brain tissue components or against antigens shared by histiocytes and microglia. This autoimmune response may persist even when all Langerhans histiocytes have been cleared from the brain lesions. This autoimmune hypothesis is supported by the absence of Langerhans histiocytes in neurodegenerative brain lesions noted in earlier studies and the similarity of these lesions with those found in paraneoplastic syndrome.

Treatment of CNS–LCH involves the agent used to treat patients with LCH without neurologic involvement. These regimens include a variety of systemic agents such as prednisone, chemotherapeutic agents like vinblastine, etoposide, cyclophosphamide, vincristine, and methotrexate, either alone or in combination. These treatment options have until recently been considered ineffective in patients with neurodegenerative LCH because patients have developed signs and symptoms of CNS LCH while on these medications. Cladribine (2–CdA) has been proven effective for treating CNS mass lesions.

Another treatment modality for CNS–LCH is radiotherapy (RT). It was used for decades in the treatment of LCH and was proved to be effective even at low RT–
doses. Greenberger et al. conducted a single–center study of 127 patients with LCH treated in a multimodal approach consisting of surgery, RT, and chemotherapy. Twenty—one of their patients were irradiated for diabetes insipidus, and four of them reached complete remission. The recommended dose for RT is irregular, and an exact dose—effect relationship has not been established yet. Doses applied are ranging from 1.4 Gy up to 45 Gy in children and 10 to 20 Gy in adults. The incidence of RT—related toxicity was extremely rare, including both acute and long—term side effects. The major concern of the RT is the development of secondary malignancies such as leukemias, teratoma, malignant meningiomas, and osteosarcomas. It was reported by Greenberger et al. to be at a rate of 3.9%. This risk is not as high as it was previously because of the improvement in the RT techniques and lower doses used in the management.

Conclusion:

The presence of empty sella turcica in neuroimaging could be the first sign of intracranial disease with chronic intracranial hypertension associated with LCH. This is especially correct if previous CT scan of the brain was normal with normal appearance of the pituitary gland and the sella. Neuroimaging films should be reviewed by an expert neuroradiologist. In patients with new neurological symptoms who were diagnosed previously with LCH, intracranial disease has to be excluded. The workup in such case should include an MRI of the brain, CT of the brain and temporal bones, bone scan, CSF analysis, ophthalmological assessment, and measurement of intracranial pressure. In patients with LCH who present with symptoms and signs of raised intracranial pressure, the term idiopathic intracranial hypertension should not be applied until an intracranial disease has been excluded totally.

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